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STUDIES OF BLOOD FORMATION IN THE FETUS AND NEWBORN.

III. THE RELATION OF ANTI-ANEMIC PRINCIPLE. ASSAY OF FETAL LIVER AND PLACENTAL EXTRACTS IN CASES OF PERNICIOUS ANEMIA AND IN MOSQUITO LARVAE.*

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IN earlier papers,[29a,b] in which the number, size and other morphologic characteristics of the red corpuscles of the fetus were described, it was pointed out that the changes which occur in the blood of the fetus as it develops, are very similar to those which are found in cases of pernicious anemia during the period of response to an effective, continuous and extremely potent stimulus to blood formation. Because of this similarity, it was suggested that the anti-anemic principle of Castle, which causes the increase in number and the decrease in the size of the red corpuscles in pernicious anemia, may be the same or very similar to the substance which

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causes the blood of the fetus to develop in the manner described. Since this principle is thought to be formed by the interaction of a factor in the diet and a secretion from the stomach,[4] it seemed plausible that it should be lacking in the fetus except insofar as it might be supplied by the mother. The utilization by the fetus of anti-anemic principle derived from the mother would explain the development of pernicious anemia of pregnancy, and deficiency of this substance in the fetus might explain some of the anemias of newborn and premature infants.

The purpose of this communication is to report the results of investigations seeking to determine the relationship between fetal hematopoiesis and that observed in cases of pernicious anemia treated with liver.

Gastric Function in the Fetus and Newborn. While the functional state of the stomach in the fetus and newborn, in view of Castle's hypothesis,[4] is a matter of considerable interest, it is a subject which has not been completely explored. Nor is it one which lends itself readily to investigation.

Kirk[16] studying in Bensley's laboratory the histogenesis of the gastric glands of the pig, found that the gastric epithelium, derived from the endoderm, remains as a single layer of cells. The embryonic gland cells which can be seen at the 2 cm. stage (10 days) constantly differentiate. Some of these become parietal cells. By the 6 cm. stage (44 days) mucus cells are found. At the 19 to 20 cm. stage (84 to 88 days) zymogenic and serous chief cells appear. In the pig at 7 cm. (about 49 days) certain definite gastric regions become differentiated. Cytodifferentiation is practically complete in the pylorus at 9 cm. (54 days) although the size of the cells, the depth of the goblets and other details alter somewhat after this. According to Kirk, the fundus is moderately well differentiated by the 19 cm. stage (85 days), but in the cardia cytodifferentiation is not complete even at birth (114 days).

The development of the gastric mucosa in other mammals and in the human embryo is apparently similar to that in the pig, although, it seems, the details have not been as thoroughly studied as in this animal. In the human embryo[20] at 42 mm. (about 71 days), elaboration of mucus may be observed. In the 120 mm. embryo (114 days), parietal cells and zymogenic cells can be distinguished. The pyloric and cardiac portions of the stomach become differentiated between the fifth and sixth months[15] but even at birth the full number of glands is not present.

The gastric ferments in the embryo and newborn received early attention. In 1874, Zweifel[31] reported that pepsin is present in the gastric mucosa of the newborn, and also found this ferment in the stomach of a premature infant. Grützner's preliminary investigations[10] indicated that the stomach of embryos of the sheep, cow, pig and dog contains small traces of pepsin but no acid. He found

that the pepsin content increases as the fetus develops. Moriggia[21] found an acid reaction and evidence of digestive activity in the "labmagen" of the cow embryo as early as the third month. Hammarsten[11] could demonstrate no peptically active substances in the stomach of dogs during the first 2 weeks of life but the gastric secretion at birth contained sufficient acid to coagulate milk. His findings in newborn kittens and rabbits were similar to those in dogs. Wolffhügel[30] who confirmed these results, was uncertain whether the acid present was lactic acid or free hydrochloric acid. Gmelin[7] claimed that there is only lactic acid in the stomach of pups at birth, but Cohnheim and Soetbeer[5] in sham feeding experiments found free hydrochloric acid as early as the first day. Langendorff[18] found trypsin even though pepsin was absent in newborn dogs and cats. In the rabbit, however, even in young embryos, Langendorff demonstrated both of these enzymes and van Puteren[22] found that acid appears in the stomach of rabbit embryos in the last third of the developmental period.

Langendorff[18] studied several hundred embryos of the pig and found traces of pepsin in the gastric mucosa as early as the 120 to 135 mm. stage (63 to 67 days), as well as larger amounts in later stages (170 to 190 mm., 77 to 85 days). The amount during intrauterine life was never great, however, and showed individual variations. He described the contents of the stomach as tenacious mucoid material, devoid of acid and lacking pepsin even when the enzyme could be demonstrated in the mucosa. Langendorff found pepsin also in the gastric mucosa of fetuses of the cow and the rat.

In the human fetus, according to Langendorff[18] pepsin appears at the end of the third or the beginning of the fourth month and after this it is quite plentiful. In two fetuses of 150 and 170 days, respectively, the writer found 1.5 cc. of watery fluid in the stomach which gave a yellow reaction with di-methyl-amino-azobenzol. In the stomach of the older fetus, there were 12.5 units of combined acid. From the stomachs of several other fetuses no fluid was obtained. Extensive studies[12] of the gastric secretion of newborn infants before they were given food were reported by Hess, who found considerable amounts of hydrochloric acid. Rennin, pepsin, and lipase were also obtained.

In pups and kittens Sutherland[25] found no spontaneous secretion of gastric juice *in utero*, but did find some secretory response to gastrin when the fetuses were within a few days of term. The secretory response to gastrin increased with age, at least for the first few days. In guinea pigs, Sutherland discovered that there may be a spontaneous secretion of acid gastric juice during late intrauterine life. In newborn rabbits the gastric juice contained hydrochloric acid on the second day after birth.

Gastric motility appears early in fetal development. Tani[26] found that spontaneous movements occur in the stomach of the rab-

bit fetus when the body weight has reached 7.5 gm. and Koshtoyantz and Mitropolitanskaya[17] claimed that automaticity in the fetal human gastro-intestinal tract develops after the seventh week. Recently Friedman[6] reported that spontaneous contractions of the stomach of the cat fetus are already present in fetuses of 58 mm. body length (about 30 days). In older fetuses the customary reactions to drugs such as pilocarpine and atropine occurred.

Heuser's[13] observations in the opossum indicate that the fetal stomach in this species is capable of physiologic activity before its cytologic development is complete. The fetuses appear in the pouch as early as 10 days after the beginning of segmentation. Five days before birth the digestive tract of the opossum is no further advanced than it is in the 3-day chick embryo. At birth, the gastric glands are not developed and the epithelial cells are yet of a simple type. Nevertheless milk is digested.

It is thus evident that physiological activity may be possible in the stomach before birth. Whether this actually occurs is unknown and what bearing this would have on hematopoiesis in the fetus is likewise unanswerable. There is no information concerning the elaboration of "intrinsic factor" in the fetus nor do we know whether there is a source of "extrinsic factor." The content of amniotic fluid in this respect is unknown. It must be admitted that the formation of anti-anemic principle by the fetus itself is a possibility which cannot at the present time be dismissed. In the light of our present knowledge, it would seem more probable, however, that if the fetus requires anti-anemic principle, it derives this substance from the mother. In any event, precursor substances would ultimately be drawn from her.

Direct evidence bearing on these questions is difficult to obtain, but indirectly the following experiments may be of some significance.

The Effect on the Blood of the Fetus of the Administration of Liver Extract to the Mother and to the Fetus. Rabbits were mated in the laboratory and liver extract (Lilly 343, N.N.R.) was given intramuscularly, 5 cc. twice weekly. All of the animals appeared to be in good health and were given the same food. Three rabbits received liver extract, whereas 4 were used as controls. No appreciable change was observed in the red cell count, hemoglobin, mean corpuscular volume or reticulocytes of any of the pregnant animals.

Fetuses of equal age were removed from rabbits given liver extract and from control animals. Study of their blood suggested that no effect on the fetal blood is produced by the administration of liver extract to the mother. Thus the red cell counts of two fetuses of 21 days taken from a rabbit given liver extract, were 2,770,000 and 2,860,000 respectively, with mean corpuscular volumes of 108 and 109 cubic microns. The red cell counts of two fetuses of this age taken from a control rabbit were 3,400,000 and 3,240,000 respectively with mean corpuscular volumes of 112 and 115 cubic microns. These differences are no greater than those we have observed in fetuses from different mothers.[29a,b]

An attempt was also made to inject liver extract directly into the placenta. This was done by laparotomy, liver extract being injected into each placenta in one horn of the rabbit uterus, while no injections were made in the other horn. As might be expected, usually the fetuses died or were aborted. In one instance, however, 0.15 cc. liver extract (Lilly 343, N.N.R.) was injected on the tenth day of pregnancy into each placenta in the left horn of the uterus and the fetuses remained viable. Thirteen days later, hysterectomy was performed. The average red cell count of the fetuses in the right horn was 2,140,000 and the mean corpuscular volume was 150 cubic microns, whereas in the fetuses from the left horn an average erythrocyte count of 2,320,000 and mean corpuscular volume of 154 cubic microns were found. These differences were regarded as too small to be significant.

These experiments were not continued, not only because of their difficulty, but also because it was felt that a failure to influence the blood of the fetus by the administration of liver extract could not be interpreted as contradicting the hypothesis proposed. If it is assumed that the fetus already receives a maximal quantity of anti-anemic principle, then any additional amount cannot be expected to produce a demonstrable effect.

Anti-anemic Potency of Fetal Liver. In the adult mammal, particularly in swine, cattle and man, anti-anemic principle is found in the liver, where it is probably stored. This substance is not found in the liver of cases of pernicious anemia in relapse[14] and following total gastrectomy in the pig the anti-anemic potency of the liver becomes progressively depleted.[1,9] In a consideration of the rôle of Castle's principle in fetal hematopoiesis, information concerning the anti-anemic potency of fetal liver is thus of fundamental importance.

Berglund and his associates[2] fed powdered fetal calf liver, 300 gm. daily, to one patient with pernicious anemia. No reticulocyte response followed but the erythrocyte count rose. The latter change, however, might possibly have been the effect of an extract of adult liver given during the preceding 9 days which had been associated with a very slight reticulocyte response. Bence[1] stated that an extract made of the fetal liver of beef was as potent as extract made from adult liver and used this as evidence favoring his opinion that an interaction between two factors is unnecessary for the formation of anti-anemic principle. He seems, however, to have tested the fetal extract in one case only. Following injection of this extract, the reticulocytes rose irregularly to a maximum of 19% and the erythrocyte count, which was as low as 1 million, did not change. This cannot be considered to be incontrovertible evidence of the presence of anti-anemic principle in fetal liver and at best indicates that the quantity present is less in fetal than in adult liver. He also reported that an extract made from the liver of a suckling calf, given to a patient with less than 1 million erythrocytes, was associated with an increase in reticulocytes to 46% and a distinct rise in red cells and hemoglobin.

More convincing as regards the presence of anti-anemic principle in fetal liver is the report of Goldhamer *et al.*[8] who made an extract of the liver of a 7-month human fetus. Twenty cc. of this extract, representing 65 gm. of fresh liver, produced an increase in reticulocytes to 17.6% in a patient whose erythrocyte count was 950,000 per c.mm. This was, however, quite clearly a submaximal response.

Method. For our own observations, the pig was chosen as the source of fetal liver. This was done not only because pig fetal liver was obtainable in adequate amounts but also because it has been demonstrated that, as regards the formation of anti-anemic principle, this animal may be compared with man. Desiccated hog's stomach is potent in the treatment of pernicious anemia[24] and commercial liver extract (Lilly, 343 N.N.R.) is made from pork livers. Furthermore, as already pointed out, it has been shown that the anti-anemic potency of adult pig liver becomes greatly reduced following total gastrectomy.[1,9]

The fetal liver was prepared as an extract for parenteral injection because, even though this entails a loss of 20 or 25% of the original potency of whole liver, the effectiveness of active material given by injection is very much greater than that given by mouth. The extracts were made in the Research Laboratories of Eli Lilly and Company by a modification of the method by which commercial extract derived from adult liver is prepared. The livers of fetuses of the second third of the gestation period (45 to 165 mm.) were used in the preparation of extract T 670; those of the third third (166 to 250 mm.) formed extract T 671; those of the fifth sixth are represented by extract T 702; and those of the sixth sixth, by T 703. Like the commercial product (Lilly, N.N.R.), these extracts were prepared in concentration such that 1 cc. represented 5 gm. of original fresh liver tissue.

Bence[1] pointed out that extract made from the livers of gastrectomized hogs is light opalescent in color rather than brown as is that made from normal liver. It is interesting to note that all of the fetal liver extracts were lighter in color and lower in the content of solids than extract made from adult liver. Whereas the latter is very dark and not transparent, with a content of 19 to 21 gm.% solids, extract T 670 was watery in appearance except for a dull yellowish color (solids 4.63%); T 702 was similar in appearance but slightly darker (solids 5.05%); T 671 was still darker (solids 7.63%); while T 703 was moderately dark and more nearly resembled 343 although it was quite transparent (solids 8.10%).

The extracts were assayed by giving uniform doses daily for periods of 6 to 15 days to cases of pernicious anemia during the stage of relapse. They were usually administered intramuscularly but in one instance extract was injected intravenously. Following the trial periods with fetal liver extracts, uniform daily doses of commercial Solution Liver Extract, Lilly N.N.R. were given. No other anti-anemic therapy was used. Reticulocyte counts were made daily and erythrocyte counts, hemoglobin and volume of packed red cells were determined at 5-day intervals.

Results. The results of this assay are summarized in Table 1. In Patient E. M., extracts T 670 and T 671 were ineffective in doses of 1 cc. for 10 days each, whereas extract made from adult liver caused a definite, though submaximal[3] response. In Patient O. M., studies were less satisfactory because assay of fetal liver extracts could only be commenced after a response had already been obtained to adult liver extract. This patient's condition on admission was so serious that 20 cc. of Solution 343 (Lilly N.N.R.) was given. Administration of fetal liver extracts was commenced 21 days afterwards, at a time when the reticulocytes had again reached a low level and the erythrocyte counts had ceased to rise. In this

patient, as in E. M., doses of 1 cc. for 10 days of extracts T 670 and T 671 proved ineffective and the patient's condition became less satisfactory. It must be observed, however, that a clear cut response to Extract 343 in these doses did not immediately follow and an increase in the erythrocyte count occurred only after continued treatment with extract of adult liver.

In Patient T. E., T 670 again proved ineffective in these doses, as did T 702 and T 703. Adult liver extract was followed by a satisfactory response. Exact comparison of the potency of adult and fetal extracts cannot be made in this case, however, because the patient's condition by this time necessitated the administration of doses of adult liver extract which were considerably larger than those of the fetal extracts.

In G. A. C., T 670 in doses of 3 cc. had no effect whereas 343 in this dosage was followed by a maximal response. Extract T 702 was given to Patient B. D. in 10 doses of 3 cc. each. There was no reticulocyte response, nor did the hemoglobin or volume of packed red cells change although the erythrocyte count rose. Administration of extract 343 was followed by a maximal reticulocyte response.

Patient L. E., received extract T 703 in 6 doses of 10 cc. each. During this period the successive daily reticulocyte counts were 0.5, 0.9, 1.2, 0.7, —, and 0.7%. On the sixth day after administration of this extract had been commenced, the reticulocytes were 1.5%. Further observation without other treatment would have been desirable but this was not possible and administration of an extract (J. H. H.) prepared at this hospital from adult liver was commenced on this day. The reticulocyte counts on the succeeding days were 1.2, 1.3, 1.8, 5.4, 7.2, 7.2, 8.9, 8.9 2.1, 0.7, and 1.3%. Whether there may have been a very slight, delayed response to T 703 cannot be decided, but at least it was insignificant when compared with the effect of the extract made from adult liver.

The ineffectiveness of extract T 703 was further demonstrated in Patient I. G., who received 9 doses of 3 cc. each and 3 doses of 10 cc. each. Administration of this extract was commenced 5 days following a single dose of 3 cc. adult liver extract which had no apparent effect and could not be considered to have prevented the appearance of a response to T 703. Following the administration to the patient of another extract of unknown potency, the injection of adult liver extract in doses of 1 cc. daily was followed by a well marked reticulocyte response.

As a final test of extract T 703, it was administered *intravenously* to Patient E. N., in 10 doses of 10 cc. each. This was entirely without effect (Table 1 and Figure 1).

Assay of these fetal liver extracts indicated quite clearly, then, that they were of no value in the treatment of pernicious anemia. The extract derived from the livers of pigs in the second third of the gestation period (T 670) was ineffective when given intramuscularly in 10 doses of 3 cc. (Patient G. A. C.), as well as in smaller doses (Patients E. M., O. M., T. E.), although extract made from adult liver caused a maximal response when given in 3 cc. doses (Patient G. A. C.). Administration of extract made from the livers of pig fetuses in the last third of the gestation period (T 671) which was administered only in 1 cc. doses (Patients E. M. and O. M.) was associated with a very irregular, probably non-specific, reticulocyte variation in 1 patient and with no change in reticulocytes in another.

The anti-anemic potency of the livers of fetuses of the last third of the gestation period was tested further by using extracts made

TABLE 1.—SUMMARY OF RESULTS OF ASSAY OF FETAL LIVER AND PLACENTAL EXTRACTS IN CASES OF PERNICIOUS ANEMIA.

Patient.	Period one.						Period two.						Period three.						Period four.					
	Extract.		Blood.				Extract.		Blood.				Extract.		Blood.				Extract.		Blood.			
			R. B. Cs.		Retics.				R. B. Cs.		Retics.				R. B. Cs.		Retics.				R. B. Cs.		Retics.	
	No.	Dose cc. x days.	Initial.	At end of period.	Initial.	Highest.	Day* of peak.	No.	Dose cc. x days.	Initial.	At end of period.	Initial.	Highest.	Day* of peak.	No.	Dose cc. x days.	Initial.	At end of period.	Initial.	Highest.	Day* of peak.	No.	Dose cc. x days.	Initial.	At end of period.	Initial.	Highest.	Day* of peak.
E. M.	*T 670*	1 x 10 i.m.	2.08	1.82	0.4	0.6	5th (10)	*T 671*	1 x 10 i.m.	1.82	1.76	0.3	2.3†	3rd (18)	*343*	1 x 9 i.m.	1.76	2.22	1.0	4.9	9th (34)	*343*	5 x 8 i.m.	2.22	2.65	4.1	*7.0*	2d (37)
O. M.	*343*	10 x 2 i.m.	0.47	1.93	2.6	*46.2*	5th (6)	*T 670*	1 x 10 i.m.	1.93	1.90	0.6	0.8	7th (29)	*T 671*	1 x 10 i.m.	1.90	1.95	0.4	0.7	8th (40)	*343*	1 x 10 i.m.	1.95	1.85	0.5	1.2	15th (47)
T. E.	*T 670*	1 x 10 i.m.	2.14	2.00	0.7	0.8	4th (8)	*T 702*	1 x 10 i.m.	2.00	1.59	0.7	0.7	6th (20)	*T 703*	1 x 7 i.m.	1.59	1.20	0.1	0.4	3rd (27)	*343*	10 x 3 i.m.	1.20	..	0.4	*20.0*	4th (35)
G. A. C.	*T 670*	3 x 10 i.m.	2.18	2.09	0.8	0.9	7th (8)	*343*	3 x 12 i.m.	2.09	2.70	0.6	*13.8*	8th (19)	*343*	5 x 19 i.m.	2.70	4.22	6.7	1.2	10th (29)							
B. D.	*T 702*	3 x 10 i.m.	3.12	3.49	1.1	1.3	5th (9)	*343*	3 x 10 i.m.	3.49	3.46	1.0	*5.1*	7th (21)														
L. E.	*T 703*	10 x 6 i.m.	1.70	1.75	0.5	1.5	6th (8)	*J. H. H.*	10 x 16 i.m.	1.75	2.07	1.5	*8.9*	7th (15)														
I. G.	*343*	3 x 1 i.m.	2.02	2.15	1.5	1.1	5th (6)	*T 703*	3 x 9 10 x 3 i.m.	2.15	2.13	1.1	0.1	12th (18)	*T 746*	5 x 3 7 x 5 i.m.	2.06	1.86	0.1	0.5	6th (27)	*343*	1 x 10 i.m.	1.86	2.06	0.3	*8.4*	8th (37)
																						343	3 x 10 i.m.	2.06	2.74	1.8	*16.1*	6th (45)
E. N.	*343*	5 x 3 3 x 5 i.m.	0.80	1.43	0.6	*24.0*	6th (6)	*T 748*	5 x 5 10 x 10 i.m.	2.46	2.62	0.2	0.3	4th (35)	*T 703*	10 x 10 I.V.	2.60	2.73	0.1	0.4	7th (49)	*T 747* *T 748*	10 x 3 10 x 1 I.V.	2.73	..	0.2	0.3	5th (57)
																							E. N.: Period Five					
																						343	10 x 5 3 x 6 i.m.	2.78	3.75	0.2	*3.9*	9th (68)
J. F.	J. H. H.	10 x 1 I.V.	1.15	2.50	0.8	*28.0*	5th (6)	*T 747*	5 x 7 10 x 6 i.m.	2.56	1.90	0.8	0.9	9th (26)	*343*	10 x 9 i.m.	1.90	2.33	0.6	9.5	6th (35)							

Details will be found in the text; "i.m." refers to intramuscular, "I.V." to intravenous administration.

* The day given is that on which the highest reticulocyte count which followed administration of the stated extract was found. The number in parentheses indicates the total number of days of observation up to the time of this reticulocyte count.

† This increase was very irregular and probably does not represent a specific response.

from the livers of the fifth sixth (T 702) and the sixth sixth (T 703) of the gestation period. The former was ineffective in 3 cc. (Patient B. D.) as well as in 1 cc. doses (Patient T. E.) whereas the latter, tested in 4 patients, was not only ineffective in doses as high as 10 cc. intramuscularly (Patient L. E.) but even when administered intravenously in ten 10-cc. doses, was associated with no changes in the blood (Patient E. N.).

Assay of Placental Extracts. The content of anti-anemic principle in the placenta is a matter of obvious significance in regard to the suggestion[29a] that anti-anemic principle may pass from the mother to the fetus and thus influence fetal blood formation. It has been stated that the placenta, like the brain and kidney possesses some anti-anemic potency[19] but the recorded evidence is by no means conclusive. Consequently, extracts were made, in the laboratories of Eli Lilly and Company, of the placenta of pigs during the second third, the fifth sixth, and the sixth sixth of the gestation period. No precautions were taken to free the placenta of blood since the anti-anemic principle not improbably is carried in this medium.

The extracts were made by a modification of the method by which Solution Liver Extract (Lilly, 343 N.N.R.) is prepared. One cc. of solution corresponded to 5 gm. of original tissue. The following extracts were used:

T 746. A pale yellow solution made from placentæ of the second third of the gestation period. Total solids 3.88 gm. per 100 cc.

T 747. Watery in appearance, with faint tinge of yellow. Total solids 1.95 gm. per 100 cc. Made from placentæ of the fifth sixth of the gestation period.

T 748. Greenish solution made from placentæ of the sixth sixth of the gestation period. Total solids 6.55 gm. per 100 cc.

All of these solutions were paler in color than the fetal liver extracts already described.

Results of the assay of these extracts are recorded in Table 1. T 746 was given intramuscularly to Patient I. G. in 3 doses of 5 cc. and 5 doses of 7 cc. Reticulocytes and blood counts remained unchanged. Adult liver extract, on the other hand, caused a well marked reticulocyte response in 1 cc. doses and a maximal effect was produced by 3 cc. doses.

T 747 was given to Patient J. F. in 7 doses of 5 cc. each and 6 doses of 10 cc. each. On admission this patient's condition was so grave that 1 dose of 10 cc. of adult liver extract was first given intravenously. This was followed by an increase of reticulocytes to 28% and a rise in the erythrocyte count to 2,500,000 cells. This was a submaximal response. Administration of placental extract was not commenced until 14 days following this single intravenous injection. At this time the red cell count, hemoglobin and volume of packed red cells had ceased to rise and reticulocytes had been below 2% for 4 days. During the 13 days during which placental extract was administered the erythrocyte count decreased while the reticulocytes remained unchanged. Subsequent administration of adult liver extract in 10 cc. doses was followed by a submaximal response.

Patient E. N. (Fig. 1) received extract T 748i n five 5-cc. doses and ten 10-cc. doses. As in J. F., it was necessary to treat this patient with adult liver extract before the placental extract could be used. He received a total of 30 cc. of Solution Liver Extract 343 (Lilly N.N.R.) intramuscularly, which was followed by a reticulocyte increase to 24% and a rise of the erythrocyte count to a level of 2,510,000 cells. This effect was not a maximal

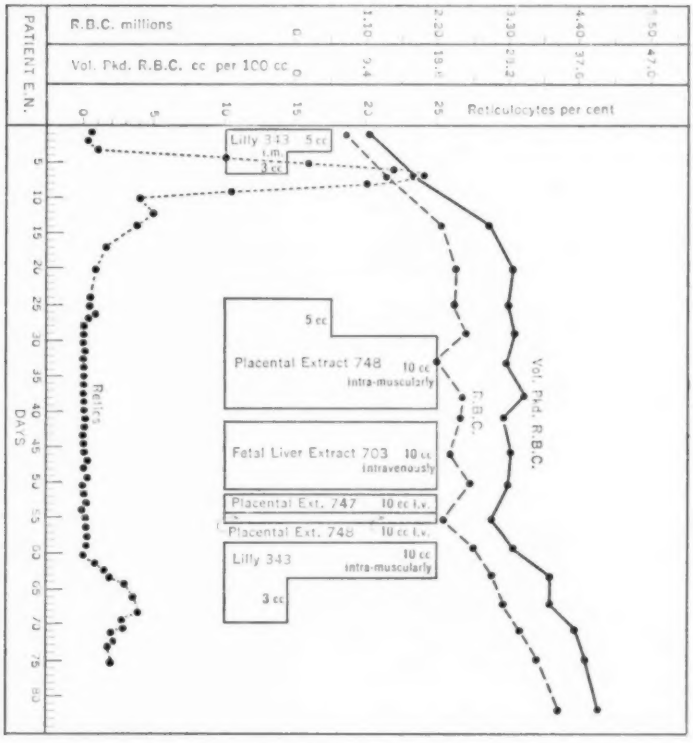

FIG. 1.—Changes in the blood of Patient E. N. as influenced by various extracts. (See also Table 1.)

response. Administration of placental extract was not commenced until 24 days following treatment with adult liver extract, by which time the reticulocytes had remained below 2% for 9 days. During the 15 days in which T 748 was administered, the reticulocytes remained at a level of 0.6 to 0.2% while the erythrocyte counts remained essentially unchanged. Following a period of 10 days during which T 703 was given intravenously without effect, T 747 was given intravenously in 3 doses of 10 cc. each and T 748 in one such dose. These injections had to be discontinued because of the patient's discomfort. Reticulocytes remained at a very low level (0.2 to 0.3%) and the erythrocyte count remained constant. Four days following the last intravenous injection, adult liver extract (Lilly, N.N.R.) was given intramuscularly. Reticulocytes promptly began to increase and the blood counts rose. The response to large doses of extract, however, was not maximal.

Like the fetal liver extracts, extracts of placenta were thus of no value whatever in the treatment of pernicious anemia. The extract of placentæ of the second third of the gestation period was ineffective when 50 cc. were given intramuscularly in the course of 8 days; that made from placentæ of the fifth sixth of the gestation period produced no effect on the blood when 95 cc. were given intra-

muscularly in the course of 13 days, or when 30 cc. were given intravenously in 3 days; the extract made from the placentæ of the last sixth of the gestation period, though not administered under ideal circumstances, should have produced some change in the blood were any potent material present, for 125 cc. were given in the course of 15 days.

Content of Growth Factor Required by Mosquito Larvæ in Fetal and Adult Liver Extracts and in Placental Extracts. Trager[27] has demonstrated that the larvæ of the yellow fever mosquito (*Ædes ægypti*) require for growth an accessory food substance contained in partly purified liver extracts rich in anti-pernicious anemia principle. He has found (unpublished work) that adult pig kidney contains as much of the growth factor as pig liver, pig heart about half as much, and pig leg muscle very little. Although the substance required by the mosquito larvæ and the anti-anemic substance are not considered to be identical, they are thought to be related. Dr. Trager kindly consented to assay the fetal liver and placental extracts for this growth factor.

Because the presence of phenol which is used as a preservative in liver preparation for parenteral use interferes with the growth of mosquito larvæ, extracts corresponding in every other way to those used in patients were prepared in powdered form without preservative (Table 2). The growth data have been expressed as the product $N \times \frac{1}{T}$ in which N equals percentage of larvæ reaching the fourth instar within 9 days, and T equals the average time required

TABLE 2.—ASSAY OF LIVER AND PLACENTAL EXTRACTS FOR ANTI-ANEMIC SUBSTANCE.

Extract No.	Gestation period.	Concentration (fresh tissue per 100 cc. of solution) gm.	$N \times \frac{1}{T}$
Liver			
T 731	Second Third	100	25.0
		50	18.4
		25	9.4
T 732	Fifth Sixth	100	23.2
		50	21.1
		25	6.7
T 733	Sixth Sixth	50	23.8
		25	22.1
		12.5	5.6
343	Adult	50	21.3
		25	21.7
		12.5	19.7
		6.2	5.3
Placenta			
T 746–A	Second Third	625	5.0
		375	7.8
		250	4.4
		125	0
T 747–A	Fifth Sixth	700	2.2
		420	0
T 748–A	Sixth Sixth	330	3.3
		198	0

by these larvæ to reach the fourth instar. The maximum value for this product is 25.

The assay indicated that the placental extract had very little mosquito growth factor, even less than had pig muscle extract. Adult pig liver contained about 20 times as much growth factor as leg muscle, and about 50 to 100 times as much as placenta. In the fetal liver extracts, less growth factor was found than in adult liver extracts, there being approximately one-fourth the quantity in the extracts of livers of the second third and the fifth sixth of the gestation periods, and approximately one-half the amount in the livers of the last sixth of the gestation period as compared with adult liver extracts.

Comment. The failure to demonstrate anti-anemic principle in fetal liver may be interpreted as further evidence favoring the comparison of the fetus with the patient suffering from pernicious anemia. The hypothesis that anti-anemic principle passes from the mother to the fetus finds no support in the failure to demonstrate anti-anemic potency in placental extracts; but on the other hand, this is not necessarily to be considered as contradictory evidence; for, unless anti-anemic principle is stored in placenta, it may not be present in quantities sufficiently large to be demonstrable by our present crude methods of assay.

The significance of the presence of growth factor for mosquito larvæ in placenta and in increasing amounts in fetal livers of the successive periods of gestation, cannot be discussed at present because the relationship of this growth factor to the anti-anemic principle is not understood.

The observations recorded, do not afford direct proof of a relationship between fetal hematopoiesis and the anti-anemic principle of Castle. Numerous questions must be answered. It may be asked whether the anti-anemic principle may not be present in fetal liver in a form which is not successfully concentrated by the method employed for the preparation of extracts of adult liver. It would be of interest to know whether any of the substance is present in fetal liver which Reimann[23] and Walden and Clowes[28] found to be present in adult liver in a form which can be made active by incubation with gastric juice. Does the desiccated stomach of the fetus possess anti-anemic potency? Can anti-anemic principle be found in other organs of the fetus? Again, if there is a deficiency of anti-anemic principle in the fetus, will macrocytic anemia of the type seen in pernicious anemia appear in newborn animals deprived of extrinsic factor? And at what age will anti-anemic principle in demonstrable amounts be found in the livers of young animals? These and related questions are the subject of study at the present time. Until they are answered no final conclusion can be reached concerning the significance of anti-anemic principle in fetal hematopoiesis.

Summary. 1. Gastric function in the fetus and newborn is discussed. Although anatomic development is incomplete at birth, it is possible that physiologic activity may commence before this time.

2. The administration of liver extract to pregnant animals and its injection into the placenta appeared to have no effect on the blood of rabbit fetuses.

3. No anti-anemic potency was found in fetal liver extracts or in placental extracts.

4. The growth factor needed by mosquito larvæ, which is found in high concentration in extract of adult liver, was present in very small quantities in extracts of placenta and in somewhat greater amounts in fetal liver extracts.

5. The observations recorded are consistent with the hypothesis that the anti-anemic principle of Castle may play a rôle in fetal hematopoiesis, but afford no direct proof of such a relationship.

The writer wishes to express his gratitude to Eli Lilly and Company, of Indianapolis, Ind., who generously prepared the fetal liver and placental extracts, and to Mr. J. P. Scott who supervised this work. The coöperation of many physicians made the assay of extracts in patients possible. Dr. H. B. Shumacker, Jr. gave surgical aid and Mr. William Schmidt and Miss Mary Paterson rendered valuable technical assistance.

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A QUANTITATIVE CYTOLOGIC STUDY OF THE BONE MARROW OF THE ADULT DOG.

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The clinical examination of sternal bone marrow is rapidly becoming an important diagnostic procedure in diseases of the blood and hematopoietic system. The history and technique of making sternal punctures and their application to clinical medicine have been reviewed recently by Nordenson[10] and Segerdahl.[15] It is assumed, of course, that the widely distributed portions of the bone marrow respond alike to any stimulus and that cytologic conditions revealed by sternal biopsy correspond essentially with those found in the marrow of other flat bones and of long bones. Alexandrov[1] (1930) studied sternal biopsies of 12 dogs, and computed the percentage distribution of the marrow cells. It is, of course, well known that changes do occur in the cellularity of the bone marrow. Marrow is spoken of as red, or cellular, and yellow, or fatty and gelatinous. Piney[13] and Custer[3] have shown that early in life the marrow of the long bones is transformed into a yellow fatty marrow, while that of the flat bones remains red; also that different bones regularly respond to increased demand at different rates. Cellularity of marrow is said to decrease with advancing years.

Although changes occur in the marrow of the shaft of long bones, wherein the active red marrow becomes yellow, there are centers or islands of active hematopoietic foci distributed throughout the fatty portions. Custer[3] has shown that the cellular density in the marrow of the long bones varies enormously in even closely adjacent regions. Bone marrow is obviously a most important organ but because of its inaccessibility very little experimental work has been done on it. The bone marrow of man constitutes about 4.6% of the body weight (Mechanik[9]); of dogs about 1.9 to 2.4% (Fairman and Whipple[4]); of rabbits from 2 to 2.59% (Nye[11]).

We undertook this comparative study of the bone marrow of the dog in order to determine whether there was any correlation in the cellular distribution in different regions of the marrow. In our study of the marrow of the rib and femur of rats,[16a] we learned that both sites are active hematopoietic centers, and that the rib excels in erythroid production but that the femur excels in myeloid activity. When unusual stress is brought to bear on the bone marrow, as in the marked stimulation which ensues on the acute hemolytic Bartonella anemia which follows splenectomy in rats, we[5] found that in spite of marked erythroid stimulation in the marrow of the

femur and rib the percentage of normoblasts was always higher in the rib.

In this study we selected, in addition to the rib and the proximal portion of the femur, which are known as active centers for production of erythrocytes, the middle portion of the femur which is usually fatty. In this way the discrete cellular foci scattered throughout the yellow marrow could be compared with the distribution found in the more active red centers.

Methods. Observations on bone marrow taken from the seventh right rib, the proximal portion of the right femur (Femur I) and of the middle of the right femur (Femur II) of 35 normal adult dogs, used for other purposes in the physiologic laboratory, form the basis of this report. All animals were normal and apparently in good physical condition. They had but recently arrived at the laboratory and had not yet been fed our adequate kennel ration. Imprint preparations of bone marrow were made immediately after death, in the manner hitherto described, and were stained by Pappenheim's modification of the May-Grünwald-Giemsa technique. In addition, small pieces of bone marrow were fixed in Helly's fluid and stained according to the method of Dominici. The abundance of fat in the marrow of the middle of the femur seemed to interfere with proper staining so that many specimens were not adequately stained and the cells could not be counted satisfactorily. In each of 35 preparations of the marrow of the rib, 33 from the proximal end of the femur, and 20 from the middle of the shaft of the femur, 500 cells were counted. All data have been handled statistically. The means of the percentage distribution of all the cells in the bone marrow, together with their probable errors, sigmas, and coefficients of variation have been determined.

Krumbhaar and Custer[7] (1935) expressed the opinion that the imprint preparations of bone marrow are not suitable for determining the relative distribution of cells, although they felt that individual cellular morphology may be best brought out by this method. They were of the opinion that cells may clump or tend to adhere to interstices of the marrow and not evenly diffuse when imprint preparations are made. We feel that this objection is probably valid when applied to the fixed cells of the marrow, such as reticuloendothelial cells, but our experience with the imprint method has led us to conclude that it is not so clearly sustained with reference to the free cells of the marrow. When we examined the marrow of the femur and rib of splenectomized rats at intervals after splenectomy for 3 months, we found a striking similarity in the percentage distribution of free cells in the marrow of the rib and femur. Likewise, when we examined the marrow of the sternum, vertebra, rib, femur and tibia of monkeys* we found percentage distributions which were essentially alike in all five regions. If errors due to technique were common, it would seem that the percentage of free cells in these regions of marrow would be less likely to be as constant as it was. If a large number of animals is used and if the number of cells counted is sufficiently large, such errors as may be due to this method will probably be eliminated.

* Unpublished data.

TABLE 1.—PERCENTAGE DISTRIBUTION OF CELLS IN THE BONE MARROW OF ADULT DOGS.

	Myeloblast.	Leukoblast.	Promyelocyte.	Myelocyte.	Eosinophilic myelocyte.	Metamyelocyte.	Granulocyte.	Eosinophil.	Heterophil.	Basophil.	Normoblast.	Lymphocyte.	Reticuloendothelial cell.	Megakaryocyte.
						In the seventh right rib of 35 dogs.								
Mean	0.51 ±0.05	1.89 ±0.11	2.83 ±0.17	8.93 ±0.36	1.15 ±0.07	15.29 ±0.47	5.06 ±0.43	2.83 ±0.23	0.14 ±0.03	0.05 ±0.01	58.98 ±1.12	1.24 ±0.06	0.99 ±0.06	0.12 ±0.02
Sigma	0.40	0.98	1.49	3.14	0.65	4.12	3.81	2.03	1.25	0.12	9.86	0.55	0.56	0.18
Coefficient of variation	78.43	51.85	52.83	35.16	56.52	26.94	75.29	71.73	178.5	240.0	16.71	44.35	56.56	150.0
					In Femur I (the proximal portion of the right femur of 33 dogs).									
Mean	0.35 ±0.03	1.51 ±0.10	2.02 ±0.12	7.24 ±0.28	1.25 ±0.09	13.34 ±0.55	4.36 ±0.36	2.19 ±0.16	0.14 ±0.04	0.07 ±0.05	64.95 ±0.96	1.15 ±0.08	1.36 ±0.08	0.09 ±0.02
Sigma	0.23	0.81	1.03	2.40	0.74	4.67	3.05	1.38	0.31	0.39	8.18	0.64	0.68	0.13
Coefficient of variation	65.71	53.64	50.99	33.14	59.20	35.01	69.95	63.01	221.41	557.1	12.59	55.65	50.00	144.0
					In Femur II (the middle of the right femur of 20 dogs).									
Mean	0.24 ±0.03	1.05 ±0.11	1.68 ±0.12	6.99 ±0.51	1.02 ±0.10	11.12 ±0.55	5.39 ±0.53	1.59 ±0.14	0.06 ±0.03	0.04 ±0.01	68.02 ±1.20	1.68 ±0.18	1.06 ±0.10	0.10 ±0.02
Sigma	0.23	0.72	0.81	3.39	0.65	3.67	3.50	0.93	0.21	0.09	7.96	1.19	0.64	0.13
Coefficient of variation	95.83	68.57	48.21	48.49	63.73	33.0	64.93	58.49	350.0	232.5	11.70	70.83	60.37	130.0

FIG. 1.—Myeloblast with basophilic cytoplasm, showing a fine nuclear pattern and three small visible nucleoli; stained with May-Grünwald-Giemsa stain. (× 1360.)

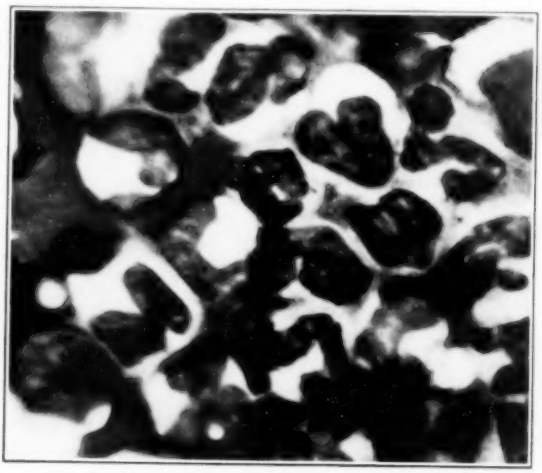

FIG. 2.—Group of myelocytes and metamyelocytes with acidophilic cytoplasm; nuclear pattern shows condensation of chromatin particles; varying stages of development are shown. (× 1360.)

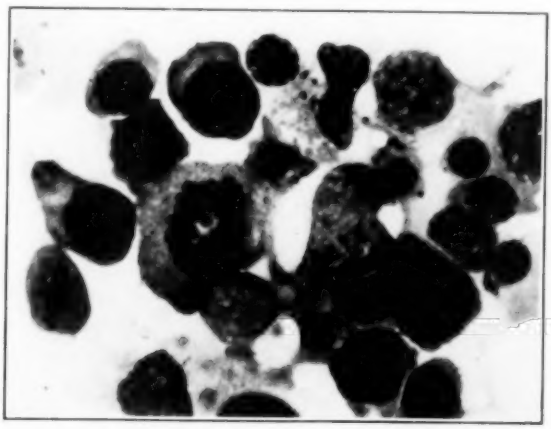

FIG. 3.—Group of erythroid cells (included in our group of normoblasts); erythroblasts, normoblasts and normoblasts with pyknotic nuclei are shown. (× 1040.)

Observations. Before contrasting the data on the cellular distribution in the marrow of the three regions studied, we submit a very brief description of the cells included in Table 1. We have followed Pappenheim's classification just as we did in our study of the marrow of the rat. We have regarded the myeloblast as the stem cell of all myeloid cells. The cytoplasm stains a deep blue, and may or may not contain azure granules. The nucleus has a very finely granular chromatin pattern and usually contains two or more distinct nucleoli (Fig. 1).

The leukoblast has a bluish cytoplasm, with a slight acidophilic change around the nucleus, and contains fine azure granules. The chromatin of the nucleus is finely divided, but there are no nucleoli such as are seen in the myeloblast.

The cytoplasm of the promyelocyte is more acidophilic and contains true small neutrophilic granules which are stained often very faintly. There is some chromatin condensation in the nucleus, giving a slightly mottled appearance to the nuclei.

The myelocyte is definitely pink and contains true neutrophilic granules. The chromatin of the nucleus is condensed, making a marked contrast with the areas of parachromatin. The shape of the nucleus is round or often slightly indented. The metamyelocyte includes those transitional forms between the myelocyte and the mature segmented granulocyte (Fig. 2). The nucleus varies in shape; the cytoplasm is pink with neutrophilic granules. We have included as granulocytes all myeloid forms with true neutrophilic granulations in which the nucleus has three or more lobulations. The pattern of the nucleus is like that described for the myelocyte.

The eosinophilic myelocyte has the nuclear pattern of a myelocyte, but the acidophilic cytoplasm is literally packed with coarse red granules. The eosinophilic granulocyte has a bilobulated nucleus, a pink cytoplasm with many red granules. The heterophilic granulocyte contains within its cytoplasm both fine red granules and coarse deep blue granules. Nuclei of these cells have a finer nuclear pattern than those of myelocytes. Basophilic granulocytes have coarse dark cytoplasmic granules and the nuclei have the myelocytic pattern with some degree of lobulation.

We have included as normoblasts all the nucleated erythrocytes from the early erythroblast to the orthochromatic normoblast with a pyknotic nucleus (Fig. 3). The erythroblasts have nuclear patterns resembling those of myeloblasts, but the cytoplasm stains a deeper blue than does that of the myeloblast. Megaloblasts were not seen in our preparations of adult marrow. Lymphocytes have a bluish cytoplasm and the chromatin of the nuclei is arranged into coarse masses. We observed a considerable number of cells with eccentric pyknotic nuclei and deep blue cytoplasmic bodies. We included these in our class of lymphocytes.

Reticulo-endothelial cells have a relatively large yellowish-blue cytoplasm with fine miniature vacuoles. The oval-shaped nucleus

has a very fine evenly distributed amount of chromatin, and nucleoli were often present. The megakaryocytes were very large cells. Their cytoplasm was blue and contained azure granules and the nuclei were large and greatly convoluted.

The data derived from our count of the cells of the bone marrow obtained from the three regions examined have been condensed into the accompanying table (Table 1) and are graphically shown in

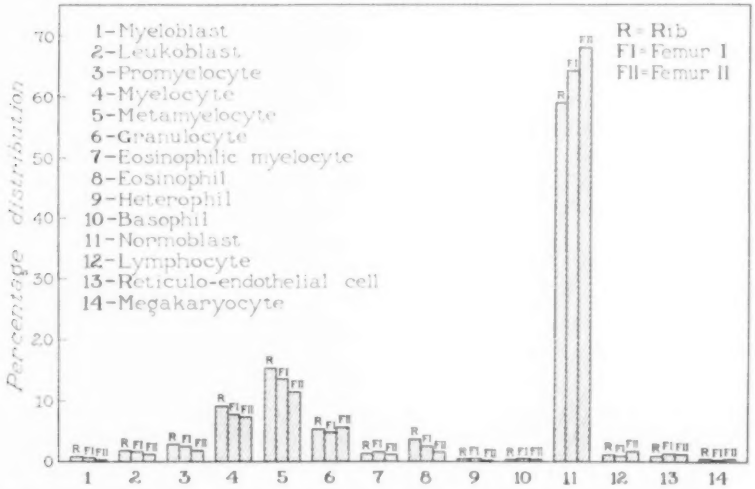

FIG. 4.—Percentage distribution of the cells encountered in the marrow obtained from three regions.

Figure 4. A survey of the table shows that there is a remarkable similarity in the percentage distribution of the different types of cells in the three regions examined, and indicates that all portions of the marrow are in general alike in their cytologic distribution. Even in preparations made from the marrow of the middle of the femur (Femur II) which is often yellow, we found essentially the same percentage distribution of the cells as we found in the marrow obtained from other regions. This indicates that the small foci seen in areas of fatty marrow are really centers of active hematopoietic proliferation. In order to appraise statistically the percentage distribution of the different cells in the marrow obtained from the three regions, we have computed the differences between the percentages found in the marrow of the rib and those found in the marrow of the proximal portion of the femur, the differences between the percentages found in the marrow of the rib and those found in the marrow of the middle portion of the femur, and the difference between the percentages found in the marrow in two regions of the femur (Table 2). In general we found a significant decrease in the percentages of the early myeloid forms in the marrow of the

middle portion of femur from those found in the marrow of the rib. There were no significant changes, however, in the percentage of mature granulocytes, in all 3 regions examined. There were significant increases in the percentage of normoblasts in the marrow obtained from the 2 sections of the femur over that found in the rib, but there was no significant difference between the percentages of normoblasts in the marrow obtained from the 2 portions of the femur.

TABLE 2.—SIGNIFICANT DIFFERENCES IN PERCENTAGE DISTRIBUTION OF CELLS IN THE BONE MARROW OF THE DOG.

Cells	Between marrow of rib and marrow of Femur I*	Between marrow of rib and marrow of Femur II †	Between marrow of Femur I and marrow of Femur II †
Myeloblast	0	+	0
Leukoblast	0	+	+
Promyelocyte	+	+	0
Myelocyte	+	+	0
Eosinophilic myelocyte	0	0	0
Metamyelocyte	0	+	+
Granulocyte	0	0	0
Eosinophil	0	+	+
Heterophil	0	0	0
Basophil	0	0	0
Normoblast	+	+	0
Lymphocyte	0	0	0
Reticulo-endothelial cell	+	0	0
Megakaryocyte	0	0	0

* Obtained from proximal portion of right femur.
† Obtained from middle of right femur.

There are some shifts in the relative distribution of total myeloid cells and erythroid cells that are of interest. In the marrow of the rib the percentage of myeloid cells (38.80%) was higher than it was in the marrow of the proximal end of the femur (Femur I, 32.56%) or in the marrow of the middle portion of the femur (Femur II, 29.28%). Conversely the total percentage of erythroid cells in the marrow of the rib (58.98%) was lower than it was in the marrow of the proximal end of the femur (Femur I, 64.95%) or in the marrow of the middle portion of the femur (Femur II, 68.02%).

The literature contains no statement of the myeloid-erythroid ratio in the bone marrow of the dog. This ratio has been described for the rabbit[14] and for man,[17,20] and we have described it for the white rat.[16a] When one contrasts the myeloid-erythroid ratio in the bone marrow of these dogs with that of man, rabbit, or rat, one may note that there is a decided shift toward the erythroid side, making the ratio less than one in all the marrow of the three regions examined.

Comment. This qualitative and quantitative consideration of the cytologic constituents of bone marrow taken from three widely separated portions of the dog lead us to conclude that there is a relative identity in the cellular organization throughout. In other

words, the appraisal of the marrow of any one region will reveal within the limits of error, what the trend of the changes are in the marrow elsewhere in the body. Sabin and Doan,[14] and Yamamoto,[19] examined the marrow of rabbits and concluded that there were no constant differences as to the extent of erythropoiesis or granulocytopoiesis in the marrow obtained from different portions of the body. Lossen,[8] Yamamoto,[19] Williams,[17] and Nordenson,[10] studying the bone marrow from different regions of individuals of different age and condition, also observed a marked similarity in the cellular distribution of the marrow. Bock [2a,b] has recently studied the function of the bone marrow in the isolated rib and thoracic vertebra, using the heart-lung preparation. He studied the cellular output in the different regions and concluded that while changes were somewhat parallel, yet granulocytopoiesis exceeded erythropoiesis in the flat bones, while the reverse was true in the long bones. Our study sustains Bock in the deduction that erythropoiesis is more marked in the long bones than it is in flat bones; in our computations the erythroid percentages were always higher than were the myeloid percentages.

The myeloid-erythroid ratio in the bone marrow of the dogs was less than one in all regions examined (Table 3). This is, of course, attributable to an increase in erythroid percentages over and above

TABLE 3.—MYELOID-ERYTHROID RATIO IN THE BONE MARROW OF THE DOG.

Source of marrow.	Myeloid cells, %.	Erythroid cells, %.	Myeloid-erythroid ratio.
Rib	38.80	58.98	0.65:1.00
Femur I*	32.56	64.95	0.50:1.00
Femur II†	29.28	68.02	0.43:1.00

* Proximal portion of femur. † Middle portion of femur.

the relative myeloid percentages. In rats, rabbits and man the myeloid percentages whenever computed, were higher than the erythroid, and the ratio always was greater than one. Alexandrov[1] computed the percentage distribution of the cells in the sternal marrow of dogs. He did not determine the myeloid-erythroid ratio. However, from his table we have computed the total myeloid and erythroid percentages and have found that the ratio was 2.08 to 1. Sabin and Doan[14] found a ratio of 2.6 to 1 in the rabbit and Young and Osgood found a ratio of 3.61 to 1 in the marrow of man. We found a ratio of 1.75 to 1 in the femur marrow of white rats. In rats in which we had induced a marked macrocytic anemia associated with a marked hepatic cirrhosis, we found myeloid-erythroid ratios less than 1.[16b] Likewise when we studied the bone marrow changes which occurred in rats after removal of the spleen, which resulted in a severe acute anemia, we also found that the myeloid-erythroid ratios were less than 1. In both of these experimental procedures we[5] had induced severe anemia. To compensate for this loss of erythrocytes, an erythroid stimulation was apparently induced in the bone marrow with a resultant increase in normo-

blasts, thus inverting the myeloid-erythroid ratio normally encountered. Young and Osgood[20] also observed significant changes in the myeloid-erythroid ratios in the marrow of patients with various pathologic conditions.

In the dogs there seemed to be an abnormal erythroid stimulation, for in all portions of marrow examined, the total number of normoblasts always exceeded the total number of myeloid cells. The dogs comprised an unselected group taken at random as they came to the laboratory. The mean erythrocyte count taken prior to their use was slightly in excess of 5,000,000, per c.mm. Kohanawa[6] (1928) and Alexandrov[1] (1930) reported more than 6,000,000 erythrocytes per c.mm., and Wintrobe and others[18] have reported that the normal erythrocyte count of dogs is 7,000,000 per c.mm. It thus is possible that our animals had fewer erythrocytes than might be expected in well nourished dogs maintained on adequate kennel rations. Such a slight anemia may well explain the stimulation normoblasts and may account for the exceedingly low myeloid-erythroid ratios. Oehlbeck, Robscheit-Robbins, and Whipple[12] produced an experimental anemia in dogs and found red cellular marrow throughout the entire long bones. In our animals the red marrow was restricted to the proximal portion of the femur; the middle portion was distinctly fatty, but contained small hematopoietic foci. It seems clear that the anemia induced by Oehlbeck and others[12] caused an excessive stimulation of the small foci in fatty marrow, resulting in a complete transformation into red marrow throughout.

Summary and Conclusions. This report covers a comparative study of the bone marrow of the ribs, the proximal portion of the femurs, and the middle of the femurs of 35 apparently healthy dogs. From imprint preparations of the marrow, 500 cells were counted in the marrow obtained at each site. The results are as follows:

1. Marrow obtained from all three regions showed essentially the same trend in the relative percentage distribution of the cells, indicating that a uniform mechanism regulates hematopoiesis in different portions of the widely distributed bone marrow. Consequently, the appraisal of the marrow of any one region will reveal what the trend of its cellular changes is elsewhere in the body.

2. All three regions of the bone marrow have been studied and the cellular data have been contrasted statistically.

3. Erythroid percentages exceeded myeloid percentages in all portions of marrow examined. The highest erythroid percentages were found in the isolated foci in the fatty marrow of the femur, and the lowest erythroid percentage was found in the marrow of the rib.

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THE BLOOD PICTURE BEFORE AND AFTER FEVER THERAPY BY PHYSICAL MEANS.*

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Our problem was to determine the effects of fever, artificially produced, on the blood picture. The device used for production of artificial fever was an air-conditioned cabinet (Kettering hypertherm). It was felt that this device offered a nearly ideal method of studying the effects of fever *per se* on various human physiologic processes.

The patient lies on an air mattress in a cabinet from which the head alone protrudes. The rest of the body is enclosed in the cabinet, which is equipped with means for the very accurate control of air temperature, relative humidity and air velocity. During this particular series of studies the patient's body was exposed for periods of from 3 to 7 hours in hot, circulating humid air. The rate of circulation of the air was approximately 450 cubic feet a minute. The temperature of the air varied between 145° and 150° F., and the relative humidity was maintained constant by means of a humidistat at 40 to 45%. Samples of blood were taken from each patient immediately before and immediately after each fever treatment.

The patients under treatment during the time these studies were being conducted suffered from the following diseases: (1) Dementia præcox, (2) gonorrheal arthritis, (3) pelvic inflammatory disease (gonorrheal), (4) chronic infectious (atrophic) arthritis, (5) chorea, (6) multiple sclerosis, (7) Parkinson's syndrome (postencephalitic),

* This study was made at the Temple University Hospital, Philadelphia, Pa. I am indebted to Dr. Frank Konzelman and his technical staff for their part in the completion of the study; to Miss Grace Doyan, R.N., for technical assistance; and to Dr. W. M. Simpson of the Department of Fever Therapy Research of the Miami Valley Hospital, Dayton, Ohio, and to Mr. Charles F. Kettering, Director of the Research Laboratories of the General Motors Corporation, for the privilege of using the Kettering hypertherm.

(8) bronchial asthma and (9) trichiniasis. No attempt will be made in this paper to evaluate the effects of fever therapy on these various diseases; all that is attempted is to present a sufficiently large number of studies to give some indication of the effect of fever *per se* on the blood picture.

Table 1 shows the results obtained when capillary and venous blood counts were made on the same individual just before and just after the production of 5 hours of systemic fever at a temperature between 105° and 106° F. This study was made to determine whether or not the high capillary counts following fever were attributable to surface hyperemia, but as there was little difference between the capillary and venous counts it was concluded that the change in the capillary count was not due to surface hyperemia.

TABLE 1.—BLOOD COUNTS BEFORE AND AFTER 5 HOURS OF SUSTAINED FEVER AT 105° AND 106° F. (GENERAL AVERAGE OF 24 TREATMENTS.)

	Capillary count.		Venous count.	
	Before.	After.	Before.	After.
Leukocytes*	6,818	13,225	6,425	13,025
Erythrocytes*	3,860,000	3,780,000	3,750,000	3,710,000
Hemoglobin†	12.0	11.8	12.5	11.9
Neutrophils, %	64	80	63	82
Lymphocytes, %	24	11	24	10
Monocytes, %	4	3	3	2
Eosinophils, %	5	2	6	2
Basophils, %	1	0	1	0

* Per cubic millimeter of blood.
† Grams per 100 cc.

Since it was felt that venous counts might be slightly more accurate than capillary counts, subsequent studies were made with venous counts alone. Table 2 gives the average venous counts for 100 patients immediately before and immediately after they received sustained artificial fevers of from 3 to 7 hours' duration at temperatures ranging from 104° to 106.8° F. It will be noted that there is a marked increase in the number of leukocytes which cannot be attributed to the concentration of blood since there is no relatively large increase in the number of erythrocytes. The slight increase in the number of erythrocytes is probably due to the concentration

TABLE 2.—AVERAGE VENOUS BLOOD COUNTS OF 100 PATIENTS AFTER SUSTAINED ARTIFICIAL FEVER. (DURATION OF FEVER, 3 TO 7 HOURS; TEMPERATURE, 104° TO 106.8° F.)

	Before fever.	After fever.
Leukocytes, per c.mm.	7,125	11,269
Erythrocytes, per c.mm.	4,460,000	4,480,000
Hemoglobin, gm. per 100 cc.	13.3	13.3
Color index	0.89	0.88
Differential count, %:		
Neutrophils	56.0	81.0
Lymphocytes	38.0	15.0
Eosinophils	2.0	1.0
Monocytes	3.0	3.0
Basophils	1.0	0.0

of blood. There is a relative increase in the neutrophils and a decrease in the lymphocytes, which also indicates that the leukocytosis is not a concentration phenomena.

TABLE 3.—AVERAGE VENOUS BLOOD COUNTS OF 52 PATIENTS AFTER 5 TO 7 HOURS' SUSTAINED ARTIFICIAL FEVER. (TEMPERATURE 105° TO 106.8°F.)

	Before fever.	After fever.
Leukocytes, per c.mm.	7,094	12,470
Erythrocytes, per c.mm.	4,340,000	4,430,000
Hemoglobin, gm. per 100 cc.	13.1	13.1
Color index	0.9	0.9
Differential count, %:		
Neutrophils	59.0	83.0
Lymphocytes	35.0	13.0
Eosinophils	2.0	1.0
Monocytes	3.0	3.0
Basophils	1.0	0.0

Table 3 shows the results of similar studies of 52 patients who were given artificial fever at the higher level of temperature and time (5 to 7 hours at 105° to 106.8° F.). It will be noted that when the 48 patients whose temperatures were lower than 105° F. for periods shorter than 5 hours are excluded, the increase in leukocytes is greater and the percentage of neutrophils become higher, whereas the percentage of lymphocytes drops.

Table 4 shows the average results of studies of samples of blood from 100 patients taken before and after sustained artificial fever.

TABLE 4.—CHEMICAL CONSTITUENTS OF BLOOD OF 100 PATIENTS AFTER SUSTAINED ARTIFICIAL FEVER FOR 3 TO 7 HOURS. (TEMPERATURE, 104° TO 106.8° F.)

	Milligrams per 100 cc. of whole blood.							
	Chlorides (oral administration of 2 to 3 liters of 0.6% solution of sodium chloride).		Sugar.		Urea nitrogen.		Carbon dioxide combining power of blood, vol. %.	
	Before.	After.	Before.	After.	Before.	After.	Before.	After.
Average in 52 cases (fever greater than 105° F.)	463	466	101.2	110.8	10.1	14.1	53	42
Average in 48 cases (fever greater than 104° F.)	462	465	95.4	99.3	12.3	14.6	57	49
Average in 100 cases (fever from 104° to 106.8° F.)	462	466	97.8	104.1	11.2	14.5	56	46

	Sedimentation time, min.		Sedimentation rate, mm.	
	Before.	After.	Before.	After.
Average in 100 cases (fever from 104° to 106.8° F.)	50.9	53.5	12.3	13.0

Temperatures were raised to 104° to 106.8° F. by means of the air-conditioned cabinet and were sustained at these levels from 3 to 7 hours. Determinations were made of the blood chlorides, blood sugar, urea nitrogen, carbon dioxide combining power and the sedimentation time. Because of the previously reported marked drop in blood chlorides due to loss of chlorides in perspiration, all of these patients were given 2 to 3 liters of a 0.6% solution of ice-cold sodium chloride during treatment. It will be seen that this amount of saline solution was sufficient to prevent any drop in the blood chlorides; in fact, under these circumstances, there was a slight increase. The increase in blood sugar and urea nitrogen are probably due to concentration of the blood. The changes in the carbon dioxide combining power of the blood and sedimentation time are of little significance but are included for the sake of completeness.

TABLE 5.—TENDENCY TOWARD AN INCREASE IN THE NUMBER OF NEUTROPHILS, A DECREASE IN MONONUCLEAR CELLS AND THE NEGLIGIBLE SHIFT TOWARD THE LEFT FOLLOWING SUSTAINED ARTIFICIAL FEVER AT 104° TO 107° F. FOR FROM 3 TO 7 HOURS IN AN AIR-CONDITIONED CABINET.

		Percentage of neutrophils.						
		Before fever.			After fever.			
Case.	No. of tests.	Immature.	Mature.	Total.	Immature.	Mature.	Total.	Shift toward
1	8	28.8	24.5	53.3	44.8	38.1	82.9	Right
2	3	40.0	18.0	58.0	57.7	9.4	67.1	Left
3	5	22.2	25.8	48.0	42.25	43.0	85.25	Left
4	8	32.5	31.1	63.6	40.4	42.8	83.2	Right
5	4	6.2	55.8	62.0	6.5	77.7	84.2	Right
6	1	2.0	40.0	42.0	17.0	67.0	84.0	Left
7	9	16.0	30.1	46.1	28.9	46.2	75.1	Left
8	8	15.5	24.5	40.1	33.0	40.2	73.2	Left
9	1	5.5	48.5	54.0	6.0	82.0	88.0	Right
10	1	25.0	21.0	46.0	41.0	40.0	81.0	Right
11	1	11.0	62.0	73.0	22.0	63.0	85.0	Left
12	1	1.0	51.0	52.0	5.0	81.0	86.0	Left
13	8	24.0	29.2	53.2	40.8	42.14	82.9	Left
14	10	23.8	30.2	54.0	32.6	47.1	79.75	Right
15	4	33.8	24.2	58.0	53.05	33.8	86.85	Left
Av. of 72 tests		19.16	34.39	53.55	31.40	50.23	81.63	Left
		Filament.	Non-filament.		Filament.	Non-filament.		
Per cent		35.76	64.23		38.46	61.53		

Table 5 gives the blood counts of 72 patients who were treated under the conditions just mentioned. This table, while showing a slight shift toward the left for the average of the 72 studies, nevertheless does not show the marked shift to the left which is present when fever is produced artificially by means of malarial inoculations. The difference of 2.7% shown in this table between the filamented and non-filamented forms before and after treatment is so slight that it may be attributed simply to statistical error. The very slight shift toward the left may therefore be considered as negligible.

Owing to the fact that the particular method which I have used for studying the blood picture has not taken into consideration the possibility of changes at other times during the period of fever and after the period of fever, and owing to the fact that Dr. Malcolm Hargraves[1] has made a special study of this particular phase of the blood picture in artificial fever therapy, I have asked Dr. Hargraves to add to this presentation a note which points out the discrepancies in my studies as compared with his own studies and makes the entire subject a little more clear.

Comment by Hargraves. In this, as in all problems, there are several lines of approach which may be used in attempting the solution. Since we have made the relationship of fever to the hemopoietic equilibrium one of our chief interests during the last few years, and since our line of approach has been somewhat different from the one employed by Dr. Krusen, he has very kindly asked us to append to his paper the following comment:

Dr. Krusen's figures on total leukocyte and differential count changes, as well as filament-non-filament ratios, are quite in accord with our work when interpreted in the light of that work. That is, Dr. Krusen's figures do not take into account the succession of changes which occur for the next 20 hours following the onset of fever and consequently, in themselves, might be misleading and mask the true postfebrile blood picture. If this period is studied with multiple, serial counts, say at intervals of a half hour, a rather constant response will be found. This response is so constant that we feel that the term "febrile hemogram" is justified. It is characterized by a postfebrile leukocytosis, the duration and extent of which is an individual affair and bears a relationship to the duration and height of fever. The peak of leukocytosis is dependent on a polymorphonuclear increase and often goes as high as, or higher than, 40,000 leukocytes per c.mm. total white blood cell count. It is here that the younger cells, as shown by a changing filament-non-filament ratio, are increased; this is evidence of bone-marrow delivery and not of a redistribution phenomenon. As the polymorphonuclear peak declines, the total count is usually sustained, or partially sustained, by an influx of monocytes. The last cell to reappear in numbers is the lymphocyte, which usually assumes lymphopenic proportions during the episode of fever.

With this picture in mind it can be seen that Dr. Krusen's figures are correct for the time of sampling, but that they usually miss the peaks of response which would have given a much greater contrast to his determinations before and after fever than his tables now indicate.

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PLASMA PROTHROMBIN LEVEL IN NORMAL INFANCY AND IN HEMORRHAGIC DISEASE OF THE NEWBORN*

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In previous work[3] we have developed a method for the titration of prothrombin in plasma. The older methods, such as prothrombin time, gave results which are known to be dependent upon many variables, and to be highly unreliable for the quantitative measurement of prothrombin. With the aid of the new technique we found that in normal adult dogs the prothrombin level varies but little from dog to dog and from day to day. More recently we have found that in man the adult prothrombin level is also rather constant but somewhat lower than in the dog. The present study shows that the value for newborn infants is only about one-fourth that of the adult human value. The rise to the adult level requires about a year.

The prothrombin level of the newborn is not only low but is also somewhat variable from case to case—facts of great interest in connection with the bleeding tendency so often seen in newborn babies. That low prothrombin values can be of importance in hemorrhagic disease of the newborn is shown in a case presented below. Prothrombin was found to be almost completely absent during the period of bleeding. Following intravenous transfusion the bleeding ceased and the prothrombin rose to and was maintained at the level seen in normal babies.

Case Abstracts of Normal Babies. Cases 1 to 9, from Obstetrical Service. Mothers' physical and laboratory examinations, including Wassermann reactions, negative. Course of pregnancy normal in all cases, except for occasional mild attacks of nausea. Routine ethylene anesthesia of less than 1 hour in each case. Babies took food normally.

Cases 10 to 19 from Pediatrics Metabolism Ward. Wassermann negative in all cases. Fed abundant milk formula diet. Cases 10, 13, 14, 18 and 19 received moderately large supplementary amounts of vitamins A and D; 16 and 17 received rather low amounts of A and D; 11 and 12 moderately low amounts of A and moderate amounts of D; 15 rather low amounts of A and very large amounts of D. All babies followed the normal weight curve and appeared to be in excellent health. Blood taken from the jugular vein or fontanelle in all cases.

* This work was made possible through the generous coöperation of Drs. E. D. Plass, John H. Randall, and Warren W. Tucker of the Department of Obstetrics; of Drs. Philip C. Jeans, Julian D. Boyd, Genevieve Stearns, and Charlotte Fisk of the Department of Pediatrics; and of Dr. Arthur Steindler of the Department of Orthopedics.

Cases 20 and 21 from the Orthopedic Service. Brought in for check-up on treatment of clubfoot.

Case 1 (M-13736). Newborn baby boy. Weight, 4065 gm.; length, 51 cm. Mother, 33 years; 6 previous pregnancies, no miscarriages. Expected date May 19; actual delivery May 29. Labor 5 hours. Plasma prothrombin (cord blood) 14% of normal adult control plasma value.

Case 2 (M-13266). Newborn baby boy. Weight, 3958 gm.; length, 50 cm. Mother, 32 years; 5 previous pregnancies, including 1 miscarriage. Expected date April 15; actual delivery May 15. Labor 3 hours. Plasma prothrombin (cord blood) 19% of adult control value.

Case 3 (M-13917). Newborn baby girl, mildly asphyxiated. Weight, 3000 gm.; length, 49 cm. Mother, 28 years; primipara. Expected date June 21; actual delivery June 4. Labor 24 hours, low forceps. Plasma prothrombin (cord blood) 24% of adult control value.

Case 4 (M-13738). Newborn baby girl. Weight, 3548 gm.; length, 49 cm. Mother, 19 years; 1 previous full term pregnancy. Expected date May 20; actual delivery May 29. Labor 6 hours. Plasma prothrombin (cord blood) 25% of adult control value. Infant blood taken by venipuncture 8 days later showed plasma prothrombin to be 44% of the adult value.

Case 5 (M-13737). Newborn baby girl. Weight, 2910 gm.; length, 51 cm. Mother, 27 years; 2 previous pregnancies, including 1 miscarriage. Expected date May 7; actual delivery May 29. Labor 6 hours. Plasma prothrombin (cord blood) 28% of adult control value.

Case 6 (M-13270). Newborn baby girl. Weight, 2868 gm.; length, 47 cm. Mother, 24 years; primipara. Expected date April 15; actual delivery May 15. Labor 28 hours. Plasma prothrombin (cord blood) 27% of adult control value. Blood by venipuncture on May 20, 5 days after birth, showed the plasma prothrombin to be 36% of the adult value.

Case 7 (M-13390). Newborn baby girl. Weight, 3000 gm.; length, 48 cm. Mother, 22 years; primipara. Expected date May 25; actual delivery May 19. Labor 24 hours. Plasma prothrombin (cord blood) 36% of adult control value.

Case 8 (M-13916). Newborn baby girl. Weight, 3006 gm.; length, 47 cm. Mother, 20 years; primipara. Expected date June 15; actual delivery June 4. Labor 24 hours. Plasma prothrombin (cord blood) 39% of adult control value.

Case 9 (M-13441). Baby boy. Birth weight, 3124 gm.; length, 48 cm. Mother, 21 years; 1 previous pregnancy. Expected date May 27; actual delivery May 20. Labor 6 hours. Baby's blood by venipuncture May 28, 8 days after birth, showed plasma prothrombin to be 27% of the adult value.

Case 10 (M-13519). Baby girl of 11 days weighing 3200 gm. Plasma prothrombin 37% of adult control value.

Case 11 (M-11951). Baby boy of 7 weeks, weighing 4650 gm. (3780 at birth). Plasma prothrombin 42% of adult control value.

Case 12 (M-11785). Baby girl of 8 weeks; weight, 4450 gm. (3202 at birth). Plasma prothrombin 42% of adult control value.

Case 13 (M-11136). Baby girl of 11 weeks; weight, 5375 gm. (3178 at birth). Plasma prothrombin 61% of adult control value.

Case 14 (M-10963). Baby girl of 12 weeks; weight, 4700 gm. (2880 at birth). Plasma prothrombin 61% of adult control value.

Case 15 (M-7819). Baby girl of 21 weeks; weight, 6030 gm. (3204 at birth). Baby isolated from mother, who has advanced chronic pulmonary tuberculosis. Plasma prothrombin 68% of adult control value.

Case 16 (M-6586). Baby girl of 28 weeks; weight, 6825 gm. (4000 at birth). Plasma prothrombin 77% of adult control value.

Case 17 (M-5886). Baby girl of 30 weeks; weight, 6520 gm. (2786 at birth). Plasma prothrombin 79% of adult control value.

Case 18 (M-4017). Baby boy of 38 weeks; weight, 8550 gm. (3800 at birth). Plasma prothrombin 88% of adult control value.

Case 19 (M-511). Baby boy of 47 weeks; weight, 9950 gm. (3968 at birth). Plasma prothrombin 100% of adult control value.

Case 20 (M-8238). Baby girl of 38 weeks; weight, 8800 gm. Congenital right clubfoot, corrected by manipulation and casts applied several months ago. Physical and laboratory examinations otherwise negative. Plasma prothrombin 85% of adult control value.

Case 21 (M-1655). Baby girl of 42 weeks; weight, 9765 gm. Congenital bilateral clubfoot, corrected during the past 6 months by manipulation, casts and lengthening of Achilles tendons. Otherwise normal on physical and laboratory examinations. Plasma prothrombin 99% of adult control value.

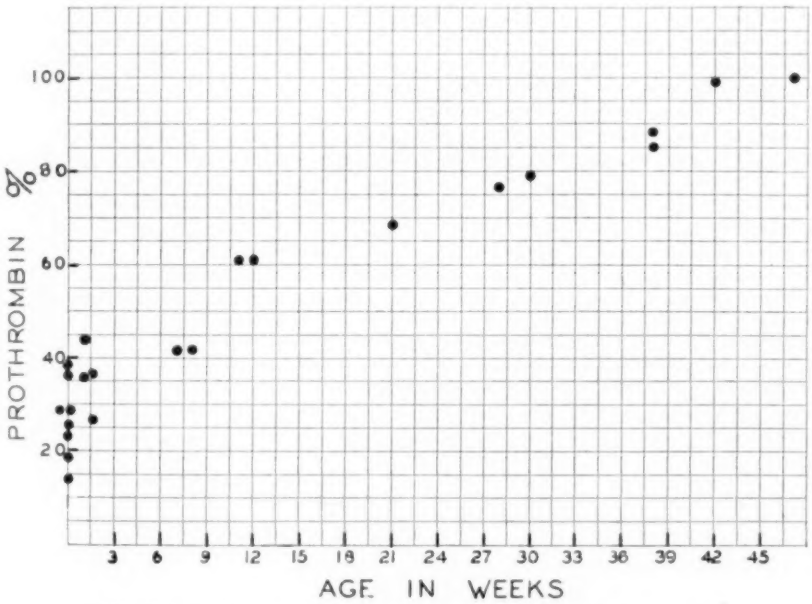

Chart I.—Plasma Prothrombin in Infants of Various Ages.

Chart I shows the plasma prothrombin values of the 21 normal infants of varying ages. The level characteristic of adult plasma is reached at the end of the eleventh or twelfth month. During the last 9 months of this period the rise is gradual, with remarkably little individual deviation from the general upward trend. The regulating mechanism appears to have become well established. In the first month of life the prothrombin values are subject to much greater variation. In the 8 newborn infants studied, the values ranged between 14 and 39% of the adult level. One of the 8 (Case 4) was bled again at the end of 8 days. The prothrombin had risen from the initial value of 25% up to 44%. A second infant (Case 6) rose from 28% up to 36% in 5 days. These 2 cases supple-

ment the statistical evidence of a steady rise in prothrombin toward adult levels.

Such variability as is present in the prothrombin level in the present series is not very clearly associated with such factors as sex, size of infant, length of gestation, or the length of labor. The series is too small, however, to rule out lesser degrees of correlation. The older infants in the Metabolism Ward were being given varying amounts of vitamins in studies being directed by Dr. Philip C. Jeans. A number of these infants, serving as controls, received average amounts of vitamins A and D. Two of them (Cases 16 and 17) received only the vitamins contained in the milk. Case 15 received very large amounts of vitamin D (10 drops viosterol 3 times a day). These dietary variations clearly had no effect upon the prothrombin level.

The earlier work on blood clotting in normal infants includes many studies on bleeding time and clotting time. The results vary somewhat with different workers, but rarely differ significantly from adult figures. The so-called prothrombin time (the clotting time of recalcified oxalated plasma) is also within normal adult limits. This clotting time, like the clotting time of whole blood, is dependent upon the amounts of antithrombin, prothrombin, and fibrinogen present. It also depends in a very striking way upon the amount of contamination by tissue juice and ruptured platelets. As we have shown,[3,2] only a relatively small part of the prothrombin normally present is needed to give a normal clotting time, provided the other clotting factors are properly adjusted. The prothrombin time, dependent as it is on many variables, is not a reliable measure of the prothrombin present, and conclusions based upon it must be discounted.

We have studied the plasma prothrombin level in a number of pregnant women and have found no significant deviation from that of non-pregnant women. Two cases studied shortly before delivery showed values of 100 and 93% of the non-pregnant control. Three, each taken a few minutes after delivery, were 110, 99, and 98%. It is evident that the fetal prothrombin level lacks the stability of that of the mother, and that the two levels are not related in any very simple way.

A Case of Hemorrhagic Disease of the Newborn. (M-13179). A patient of Dr. John H. Randall. Mother a primipara, aged 29. Congenital heart disease recognized since age of 4. No frank decompensation. Occasional epistaxis in childhood; none since. Expected date of delivery June 8. Vomiting began April 15, increased in severity. Patient was put on a diet low in protein and high in fruits and vegetables. She was given glucose intravenously. She had some luminal as sedative. No other drugs. Vomitus showed some unexplained coffee-ground material and traces of fresh blood at times. Examination May 13 showed moderate edema of ankles, marked albuminuria. No pyuria, no hematuria. Blood pressure, 154/60; white count, 16,350; normal differential; red count, 5.6 million; Wassermann test negative. No fever during period of observation. Due

to evidence of toxemia and renal involvement, a Cesarean section was carried out under local novocaine anesthesia on May 13. Operation uneventful except for some excess bleeding from uterine incision. Rapid recovery. On discharge May 24, she still had albuminuria and blood pressure of 150/80.

The infant, a female, was moderately cyanotic. Weight, 2792 gm.; length, 46 cm. Did well until its cord clamp came off on the fifth day, May 16. Following this there was oozing of blood from the cord stump. The cord was sutured on 3 occasions on May 17, and each time the oozing was only temporarily checked. In an effort to stop the bleeding, baby was given 20 cc. thromboplastin (Squibb) in divided doses subcutaneously on the 19th. Later in the evening 32 cc. of blood were given intramuscularly, and approximately 50 cc. of 5% coagulin (Ciba) were administered orally in divided doses during the course of the night. Also 10 cc. coagulin subcutaneously. Treatment ineffective. Blood oozed from puncture wounds where coagulants were injected and from stab wounds in heel from which blood was drawn for studies preparatory to transfusion. At 1.45 P.M. May 20, 100 cc. citrate blood were given intravenously. Bleeding ceased promptly. Some inflammation incident to placing sutures about the umbilicus cleared up in the next few days and the baby showed uneventful recovery and was discharged June 7. Temperature normal throughout. Infant diet May 13 and 14 was diluted cow's milk plus Karo; May 15 to 28, breast milk; diluted evaporated milk plus dextrimaltose and lactic acid thereafter.

Diagnoses: Maternal congenital heart disease; maternal toxemia with renal involvement; Cesarean section; hemorrhagic disease of the newborn, cured by transfusion.

Venous blood was taken from the antecubital fossa May 20, immediately before giving the transfusion. Hematocrit showed 17.5% cell volume. The plasma fibrin by the method of Jones and Smith[3] was 392 mg. per 100 cc. The prothrombin was too low for accurate estimation. It was clearly below 5% of the normal adult value. The antithrombic activity of the oxalate plasma was determined by incubating the plasma in varying dilutions with thrombin. After a set interval the amount of thrombin left was tested by adding fibrinogen. As a control, a series of normal plasma dilutions was tested against the thrombin. By comparing the two curves the antithrombic potency in this case was found to be approximately twice that of the normal adult control plasma.

A second blood sample taken 10 days later showed a cell volume of 42.9% and the prothrombin titer was 38% of the adult control plasma.

The mother's hematocrit May 21 showed 32% cells; the prothrombin was 100% of normal.

July 3, infant's hematocrit showed 32% cells. The plasma prothrombin was 47% of the normal adult control value. The antithrombin was within normal limits.

This patient, a primipara, 29 years old, had congenital heart disease and nephritic toxemia. She was delivered by Cesarean section 3 weeks prematurely. The baby appeared normal until the fifth day, when the cord came off and blood began to ooze from the stump. This continued for 3 days, at the end of which time the hematocrit showed 17.5% cells. The prothrombin at this time was almost completely absent. A further abnormality consisted of a moderate increase in the antithrombic activity of the plasma. The plasma fibrin level was normal. Transfusion brought about prompt cessation of bleeding. Since adult blood is rich in pro-

thrombin, the transfusion was sufficient to raise the prothrombin level to about 25 or 30% of the adult value. This level, as we have shown, is normal for infants of this age. The ability of the infant to maintain such normal levels was shown by an analysis made 10 days later, at which time the prothrombin was 38% of the normal adult value. Forty-four days after transfusion it was 47%.

This case with its response to treatment supplies sound theoretical grounds for the well-known benefits of transfusion. The case also points strongly to the conclusion that lowered prothrombin is the essential cause of bleeding in certain cases of hemorrhagic disease of the newborn. The earlier qualitative work of Whipple,[4] pointing to this same conclusion, has not received general acceptance, probably because his analyses were made on blood drawn at autopsy. Several investigators more recently have given conflicting opinions concerning this disease, basing their conclusions upon the prothrombin time. As we have stated, this method cannot be expected to give significant figures regarding the amount of prothrombin present.

Our data do not permit an opinion regarding the ultimate cause of hemorrhagic disease of the newborn. It may well be that some factor occurring in the first few days of life reduces the normally low prothrombin to the bleeding level which we observed. It is equally possible that an occasional infant is born with exceptionally low values. The incidence of hemorrhagic disease of the newborn is said to be about 1 in 200 births. In a large series it might be that a few infants would reach the danger level. The great variability shown in our series of newborn infants points to such a possibility. This variability and an occasional tendency to bleed may both be the result of pre-natal factors of unknown nature.

Summary. The plasma prothrombin level in infancy was studied with the aid of a quantitative titration procedure. The level in normal newborn babies varies in this series between 14 and 39% of the level found in normal adult plasma. The prothrombin level rises gradually during subsequent months and reaches the adult level at the end of about a year. After the first few weeks of life the individual cases show very little deviation from the curve plotted through the entire group.

A case of hemorrhagic disease of the newborn studied showed the plasma prothrombin to be less than 5% of normal adult values. The antithrombic activity of the plasma was somewhat excessive, but the plasma fibrin was normal. Intravenous transfusion of blood resulted in prompt cessation of bleeding. The plasma prothrombin studied 10 and 44 days later was found to be up to the normal values for infants of that age.

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AUTOPSY INCIDENCE OF CHOLELITHIASIS.

BASED ON RECORDS OF INSTITUTE OF PATHOLOGY, WESTERN RESERVE UNIVERSITY AND UNIVERSITY HOSPITALS, CLEVELAND, OHIO.

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IN an article entitled, "Cholelithiasis in the Korean,"[2] the writer made a comparison of the autopsy incidence of cholelithiasis among Koreans with that among other races. A summary was given of 2800 autopsies (February 2, 1898, to June 2, 1927) from the records of the Department of Pathology of Lakeside Hospital, Cleveland, Ohio. To this series is now added the results obtained in 2000 autopsies (June 3, 1927, to July 21, 1935), performed at the Institute of Pathology, Western Reserve University and University Hospitals, Cleveland, Ohio. Table 1 gives a summary of both these

TABLE 1.—AUTOPSY INCIDENCE OF CHOLELITHIASIS, BASED ON RECORDS OF LAKESIDE AND UNIVERSITY HOSPITALS.
(February 2, 1898, to July 21, 1935—4800 Autopsies).

Age (years).	White. Male. No. of autopsies.	White. Male. No. with gall stones.	White. Male. Per cent.	White. Female. No. of autopsies.	White. Female. No. with gall stones.	White. Female. Per cent.	White. Total. No. of autopsies.	White. Total. No. with gall stones.	White. Total. Per cent.
0–10	438	0	0.00	334	0	0.00	772	0	0.00
11–20	113	1	0.88	65	1	1.54	178	2	1.12
21–30	238	6	2.52	183	9	4.92	421	15	3.56
31–40	375	9	2.40	257	19	7.39	632	28	4.43
41–50	492	31	6.30	228	38	16.66	720	69	9.58
51–60	394	42	10.66	168	38	22.62	562	80	14.23
61–70	232	35	15.09	105	26	24.76	337	61	18.10
71–80	102	14	13.73	41	11	26.83	143	25	17.48
81–90	8	0	0.00	6	3	50.00	14	3	21.43
91–100	0	0	0.00	0	0	0.00	0	0	0.00
Total	2392	138	5.77	1387	145	10.45	3779	283	7.49
	Negro.								
0–10	74	0	0.00	86	0	0.00	160	0	0.00
11–20	22	0	0.00	20	0	0.00	42	0	0.00
21–30	94	0	0.00	104	2	1.92	198	2	1.01
31–40	143	2	1.40	114	8	7.02	257	10	3.89
41–50	115	4	3.48	78	11	14.10	193	15	7.77
51–60	81	10	12.35	41	9	21.95	122	19	15.57
61–70	18	1	5.56	9	3	33.33	27	4	14.81
71–80	9	0	0.00	8	1	12.50	17	1	5.88
81–90	3	0	0.00	1	1	100.00	4	1	25.00
91–100	1	0	0.00	0	0	0.00	1	0	0.00
Total	560	17	3.04	461	35	7.60	1021	52	5.09
Grand Total	2952	155	5.25	1848	180	9.73	4800	335	6.98

groups, or a total of 4800 autopsies, arranged in age, sex and color groups with the number of cases having gall stones and the percentage frequency in each group. Table 2 shows the number of cases

of gall stones in each decade, with total percentages, regardless of sex and color.

TABLE 2.—AUTOPSY INCIDENCE OF CHOLELITHIASIS REGARDLESS OF SEX AND COLOR.

Age (years).	No. of autopsies.	No. with gall stones.	Per cent.
0 to 10	932	0	0.00
11 to 20	220	2	0.91
21 to 30	619	17	2.75
31 to 40	889	38	4.27
41 to 50	913	84	9.20
51 to 60	684	99	14.47
61 to 70	364	65	17.86
71 to 80	160	26	16.25
81 to 90	18	4	22.22
91 to 100	1	0	0.00
Total	4800	335	6.98

Mosher,[3] in 1901, examined the records of 1655 complete autopsies from the Pathological Department of the Johns Hopkins Hospital. Of the 1655 patients, 1037 were males and 618 females; 634 were black and 1018 were white; the color of the remaining 3 cases was not given. In 115 cases (6.94%) gall stones were present.

Hamilton[1] (1925–1929) analyzed the records of 1000 autopsies performed at the Adelaide Hospital, Adelaide, Australia. Among the 1000 autopsies, of which 675 were on males and 325 on females, gall stones were found in 106 (10.6%).

Ophüls,[4] among 3000 autopsies performed during the years 1900 to 1923, mostly at the Lane and San Francisco Hospitals, found 214 cases of gall stones (7.1%). Of 206 patients with gall stones, 139 were men (5.86% of all males) and 67 women (10.65% of all females).

In our own series of 4800 autopsies (Table 1) gall stones were present in 335 cases (6.98%). Of the 335 patients with gall stones, 155 were men (5.25% of all males) and 180 women (9.73% of all females).

Summary. An analysis of our autopsy incidence of cholelithiasis shows:

1. Gall stones are rarely found in persons under 20 years of age; only twice in 4800 autopsies.
2. There is a gradual increase in frequency from 20 years of age.
3. Gall stones are found more frequently in the white race (7.49% than in the negro race (5.09%).
4. Gall stones are found more frequently among females (9.73%: white, 10.45%; negro, 7.6%) than among males (5.25%: white, 5.77%; negro, 3.04%).

I wish to express my appreciation to Dr. Howard T. Karsner for the use of the records of the Institute of Pathology, Western Reserve University.

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STUDIES OF GALL BLADDER FUNCTION.

XIV. ABSORPTION OF SODIUM TETRAIODOPHENOLPHTHALEIN FROM THE NORMAL AND DAMAGED GALL BLADDER.*

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RECENT studies of the physiology of the gall bladder have concerned themselves for the most part with the study of the absorption and excretion by the gall bladder of the normal constituents of the bile. The method of cholecystography recommended by Graham, Cole and Copher[2] more than 10 years ago, depends upon the use of sodium tetraiodophenolphthalein. It is, therefore, important that the effect of the normal and damaged gall bladder upon this salt be known.

The failure to make the gall bladder visible† in cholecystography is interpreted to be due to: *a*, failure of the absorption of the dye from the gastro-intestinal tract; *b*, failure of the liver to excrete the dye in adequate amounts; *c*, incompetence of the sphincter of Oddi; *d*, obstruction of the cystic duct; or *e*, a degree of cholecystitis which does not permit of concentration of the dye in the gall bladder. Much clinical as well as experimental evidence confirms these interpretations.[4] The lack of concentration of the dye in the gall bladder in cholecystitis is adequately accounted for by the evidence that water is not absorbed by the damaged gall bladder or if so, is absorbed in very small amounts.[6]

Another possibility which has been suggested as an explanation for the failure to make the gall bladder visible after dye administration is the rapidity with which it may be absorbed by the damaged gall bladder.[4] This possibility is strengthened by the work of Igwanaga[3] who reported that bacterial or mechanical inflammation of the gall bladder mucosa increases the rate of absorption of phenolsulphonphthalein, methylene blue and indigo-carmine. Likewise, Winkenwerder[9] found that slight injury of the gall bladder wall resulted in the rapid absorption of the Prussian blue reagents. Experiments on the absorption of sodium tetraiodophenolphthalein from the gall bladder were reported from this laboratory by Johnston[5] in 1931. His experiments refuted the previously advanced concept[8] that the sudden disappearance of the gall bladder shadow following a fatty meal, in clinical cholecystography, was

* Aided by a grant from the Josiah Macy, Jr., Foundation.

† The Editor has taken the liberty of changing the obviously incorrect term "visualized." We try to avoid this solecism in this journal in spite of its present widespread usage, in the hope that a better term may eventually be substituted.

due to absorption of the salt through the gall bladder wall, rather than an expulsion of it through the cystic duct. He showed that a fatty meal did not increase the amount of dye absorbed from the gall bladder bile. In a series of 6 dogs, when the salt was injected into the gall bladder by a needle with the cystic duct occluded without injury to the blood or lymph vessels, from 26 to 51% of the salt was recovered from the gall bladder after 24 hours.

If it can be shown that the damaged gall bladder absorbs sodium tetraiodophenolphthalein more rapidly than the normal gall bladder, it is reasonable to suppose that this may in part account for the failure to make the diseased gall bladder visible when using the Graham-Cole method. Experiments were, therefore, devised to test this.

Our initial experiments were conducted with a method similar to that used by Johnston.[5] Essentially, this consisted of dissolving the sodium tetraiodophenolphthalein in gall bladder or hepatic bile and injecting this solution into the gall bladder lumen by needle puncture after preliminary occlusion of the cystic duct.

Histologic examination of the gall bladder removed from animals in which the dye had been so introduced showed a surprising degree of change of the gall bladder mucous membrane. The cellular change was of such extent that it was obvious that we were not dealing with a normal membrane (Fig. 2).

It was found that in those instances where the cystic vessels did not lie on the cystic duct, the duct could be ligated without the development of histologic changes in the gall bladder wall. The changes observed after injection of the dye must, therefore, have been due to the dye itself.

In the course of these experiments it was observed that when sodium tetraiodophenolphthalein was given intravenously, the hepatic and gall bladder bile did not change its normal appearance. On the other hand, when the salt was dissolved directly in the gall bladder or hepatic bile in the same quantities as those found after intravenous injection, the bile developed a dirty bluish tinge. It seems obvious then, that sodium tetraiodophenolphthalein is not excreted in the bile in the same form as it is given intravenously. It was, therefore, necessary to devise a new method for studying the absorption of sodium tetraiodophenolphthalein from the gall bladder so that at the conclusion of the experiment the mucosa would be of normal appearance.

Absorption of Sodium Tetraiodophenolphthalein from the Normal Gall Bladder. The dye was given to a dog intravenously, and either the hepatic bile was collected for the following 24 hours or the gall bladder was removed after starving the dog for 24 hours, in order to get the dye in a more concentrated form. An aliquot of the bile was analyzed for its iodine content. A known amount of this bile containing the dye was then injected into the gall bladder of a second

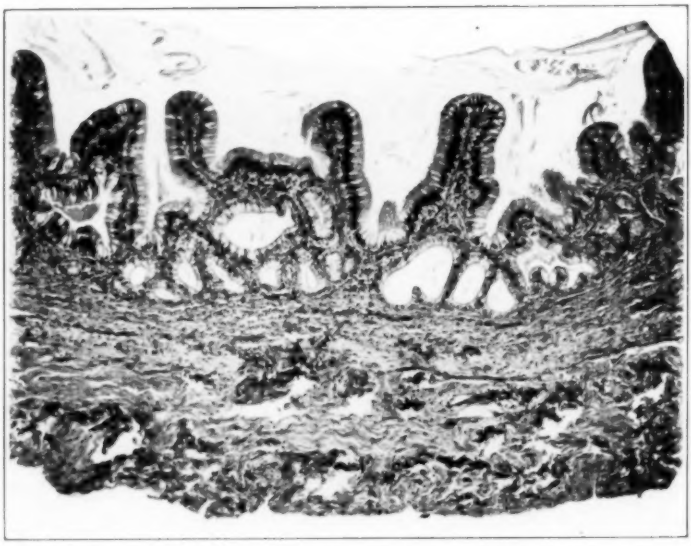

FIG. 1.—*Normal gall bladder.* Bile from a dog previously given sodium tetraiodophenolphthalein was injected into this gall bladder by needle puncture, the cystic duct having been ligated. After 24 hours the gall bladder appeared grossly and microscopically normal.

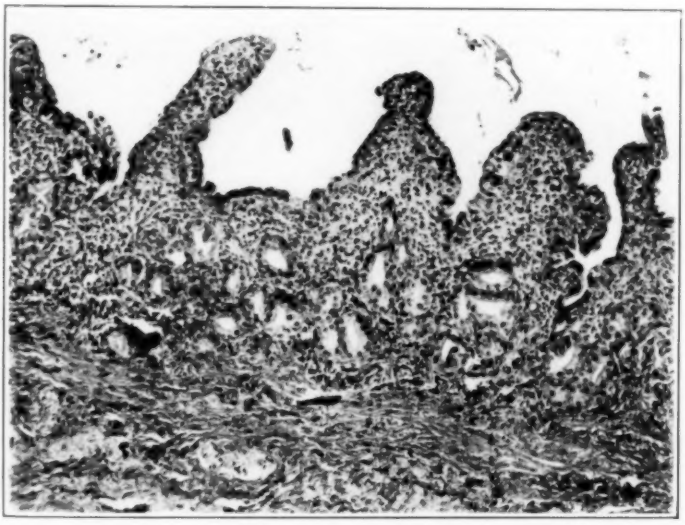

FIG. 2.—*Damaged gall bladder.* Sodium tetraiodophenolphthalein dissolved in bile was injected into this gall bladder by needle puncture, the cystic duct having been ligated. After 24 hours the damage to the mucous membrane was questionable grossly but evident microscopically.

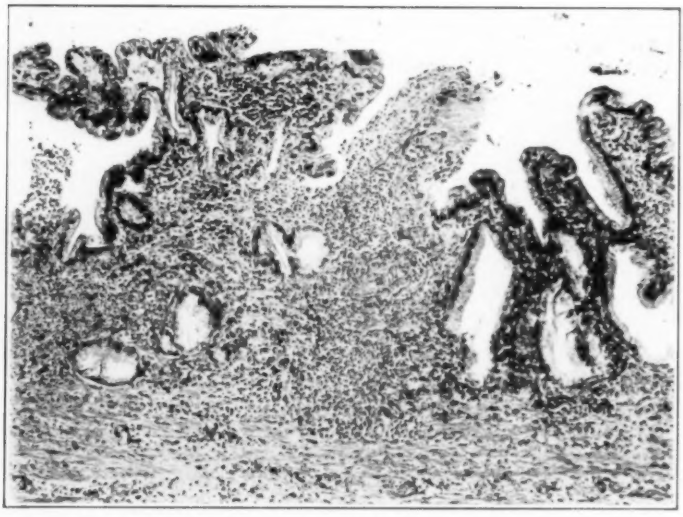

FIG. 3.—*Damaged gall bladder.* This gall bladder was intentionally damaged by injecting 5 cc. of a 10% sodium chloride solution on 2 separate days through a small rubber catheter previously placed in the gall bladder through the common and cystic ducts. The damage was evident both grossly and microscopically.

dog, by needle puncture, the cystic duct having been ligated. The dog was killed under an anesthetic in 24 hours and the contents of the gall bladder analyzed for iodine. If one were successful in avoiding the cystic blood vessels and lymphatics, the gall bladder would appear quite normal and be partly empty due to the absorption of some of its contents. The latter was, of course, more noticeable when hepatic bile was used than when gall bladder bile was used. In Table 1 are given the data from these experiments. Analysis showed that from 83 to 106% of the injected iodine was recovered from the gall bladder after 24 hours. It was not always possible to ligate the cystic duct alone. When lymphatics were included in the ligature, slight edema of the gall bladder wall was found. The mucous membrane, however, appeared normal microscopically. Such was the case in the last half of the experiments in Table 1.

TABLE 1.—ABSORPTION OF SODIUM TETRAIODOPHENOLPHTHALEIN FROM THE NORMAL GALL BLADDER.

Dog No.	Iodine as excreted by the liver, placed in the gall bladder, gm.	Iodine recovered from gall bladder after 24 hours, gm.	Percentage of iodine recovered.	Gall bladder.
61	0.139	0.119	85.9	Normal
78	.099	.097	97.0	"
723	.0278	.0257	92.0	"
725	.0278	.0295	106.0	"
798	.0966	.0901	94.0	"
799	.0157	.0137	87.7	"
157	.142	.140	98.0	"*
159	.142	.145	101.0	"*
180	.139	.115	83.0	"*
443	.051	.0462	90.0	"*
445	.102	.089	87.0	"*
503	.0645	.0646	100.0	"*

* Lymphatic vessels included in ligation of cystic duct causing slight edema of the gall bladder wall. Mucous membrane is microscopically normal.

Absorption from the Damaged Gall Bladder. This was accomplished by several different methods. As stated, the method used by Johnston[5] resulted in moderate damage to the wall of the gall bladder. The results from 5 dogs, when this method was used, showed a recovery of from 31 to 62% of the injected iodine after 24 hours (Table 2, Part A). These findings are in agreement with those of Johnston.[5]

Another series of experimental dogs was prepared by introducing a small rubber catheter into the gall bladder through the junction of the cystic and common duct, or through the common duct and thence by way of the cystic duct into the gall bladder. The central hepatic duct was ligated above the entrance of the cystic duct.[7] A gall bladder prepared in this manner will absorb its full content of physiologic saline solution when left overnight. If accessory ducts had been overlooked, bile was found in the gall bladder and the animal was discarded. The gall bladder mucosa was then damaged

TABLE 2.—ABSORPTION OF SODIUM TETRAIODOPHENOLPHTHALEIN FROM THE DAMAGED GALL BLADDER.

Dog No.	Iodine placed in gall bladder, gm.	Iodine recovered from gall bladder after 24 hours, gm.	Percentage of iodine recovered.	Gall bladder damage.
Part A—Cystic Duct Ligated, Dye Dissolved in Bile Injected into the Gall Bladder by Needle Puncture.				
39	0.0485	0.0153	31	Severe
38	.046	.0244	53	Moderate
568	.140	.0878	62	"
790	.047	.0279	52	"
956	.049	.0259	52	"
Part B—Catheter in Gall Bladder by Cystic Duct. Damaged by 10% Saline. Dye Dissolved in Bile, Placed in Gall Bladder.				
266	0.144	0.0361	25	Moderate
296	.1438	.039	27	"
347	.138	.080	57	"
911	.138	.0558	40	"
948	.138	.056	41	"
93	.141	.0499	35	Severe
122	.146	.0317	21	"
170	.1407	.0189	13	"
327	.141	.0303	21	"
Part C—Catheter in Gall Bladder by Cystic Duct. Damaged by 10% Saline. Bile, from Dog Previously Given Dye Intravenously, Placed in Gall Bladder.				
253	0.156	0.1073	68	Slight
254	.156	.0524	33	Moderate
408	.079	.0467	59	Slight
410	.079	.0292	37	Moderate
Part D—Necrotic Gall Bladder Produced by Ligating Blood Supply. Bile from Dog Previously Given Dye Intravenously, Injected into Gall Bladder.				
409	0.0515	0.0088	17	Necrotic
454	.016	.0048	29	"
471	.054	.0031	5.8	"

by injecting 5 cc. of a 10% sodium chloride solution daily for 2 or 3 days. At the end of this time, the gall bladder was found to pour out 10 to 30 cc. of turbid fluid daily. A known quantity of sodium tetraiodophenolphthalein in bile was placed in such a damaged gall bladder and the contents analyzed 24 hours later. From 13 to 57% of the injected iodine was recovered (Table 2, Part B). Gall bladder or hepatic bile obtained from a dog previously given sodium tetraiodophenolphthalein intravenously was also placed in the damaged gall bladder (Table 2, Part C). The dog at the conclusion of a single experiment was always sacrificed in order to ascertain that there was no leakage around the catheter. Grossly, the gall bladders of this group showed varying degrees of damage. In general, the more severe the histologic evidence of damage the greater the absorption of the iodine salt.

An effort was then made to produce a gangrenous gall bladder by ligating the cystic vessels so as to determine the fate of sodium tetraiodophenolphthalein under these conditions. This was done by using bile secured from a dog previously given the dye intra-

venously. From 5.8 to 29% of the injected iodine was recovered after 24 hours (Table 2, Part D). The gall bladders were necrotic, but there was no recognizable leak.

*Method of Iodine Analysis.** The iodine in the bile was determined by a hydrolytic reduction method (a modification of the method by Chiray, Lesage and Taschner[1] followed by subsequent oxidation and titration with thiosulphate. Briefly, the procedure was as follows: The sample withdrawn from the gall bladder was diluted with water to a definite volume. To an aliquot of this, containing 0.5 to 2 mg. I, NaOH and Zn powder were added and the mixture heated for approximately ½ hour. After neutralizing and filtering, H_2SO_4 is added, then Br, followed by phenol, after which potassium iodide is added and the iodine titrated with thiosulphate. Control determinations on the dye gave an average value of 50% I ± 2% in the dye, and this figure was used in calculating subsequent results. Determinations on known amounts of dye and varying quantities of bile, and also on varying dilutions of a solution of the dye in bile, gave satisfactory recoveries.

Comment. The question can be raised as to whether one is justified in regarding a gall bladder as normal when the cystic duct and a needle puncture hole have been ligated. The gall bladder, which we have designated normal, absorbed fluid and concentrated bile and appeared to be normal both grossly and microscopically (Fig. 1). In view of the marked difference in the absorption of sodium tetraiodophenolphthalein in the normal gall bladders and those which were damaged, we feel justified in regarding them as physiologically normal.

The damaged gall bladders used in these experiments may be compared to the gall bladders of acute and subacute cholecystitis as seen in man. They could hardly be said to simulate chronic cholecystitis.

The experiments on gangrenous gall bladders here reported probably have no clinical significance, since the gangrenous gall bladder in the human practically always has an obstructed cystic duct.

Summary. 1. A method has been devised to compare the absorption of sodium tetraiodophenolphthalein from the normal and damaged gall bladder of the dog.

2. From 83 to 106% of the dye was recovered from the normal gall bladder after 24 hours.

3. From 5.8 to 68% of the dye was recovered from the damaged gall bladder after 24 hours. The variation depended at least in part upon the degree of damage.

Conclusions. 1. Sodium tetraiodophenolphthalein is absorbed more rapidly from the damaged than from the normal gall bladder of the dog.

2. It is reasonable to suppose, therefore, that this factor may play some part in the failure to make the diseased gall bladder visible in clinical cholecystography.

* We are indebted to Dr. P. A. Bott and Dr. R. D. Cool of the Department of Pharmacology, University of Pennsylvania, who suggested this method.

3. Sodium tetraiodophenolphthalein is not excreted by the liver in the bile in the same form as it is given intravenously.

4. The data obtained regarding the rate of absorption of sodium tetraiodophenolphthalein by the normal gall bladder, further strengthen Johnston's[5] contention that the rapid changes occurring in clinical cholecystography must be explained upon the basis of expulsion of the dye through the cystic duct rather than absorption of the dye by the gall bladder.

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A STUDY OF THE OSSEOUS REMAINS OF THE "MOUND BUILDERS" OF EASTERN ARKANSAS.*

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A RACE of people who were sedentary agriculturists and hunters once lived along the Mississippi River and its tributaries. They erected earthen mounds of varying sizes and for this reason they have been generally referred to as the "Mound Builders." The period of their occupation of the Mississippi Valley is not definitely known. The exact relation of the "Mound Builders" to the American Indian of colonial times has not been established and it is questionable as to whether European explorers of the 16th century had any contact with them. So far as is known, the only contact the "Mound Builders" of Eastern Arkansas may have had with Europeans was with the men of DeSoto in 1539 to 1543. The explorers who visited the western bank of the Mississippi River after DeSoto and before colonization of this area, which is now the eastern part of Arkansas, were usually definite in their statements that the people they saw in this region were few in number and probably remnants of tribes.[5]

* University of Arkansas Research Series No. 413.

The accounts of these early explorers are important since they indicate that between the time of DeSoto's visit and the beginning of trade and colonization along the Mississippi and Arkansas Rivers, this area was not densely populated. The population was never great enough to support the large burial grounds which have been found in Mississippi and Crittenden Counties in Eastern Arkansas. These burial grounds, therefore, were probably made in precolonial times, that is, prior to the 17th century.

The object of this study was to determine whether examination of the bones of the "Mound Builders" would reveal lesions which are comparable to those that are recognized as fairly definite clinical entities at the present time. The skeletal material obtained from more than 400 graves was examined and the diseased skeletons were retained for further study and roentgenologic investigation of their structure. In this communication, only representative material which was well preserved will be presented. In order that the maximum of details of structure could be obtained by roentgenologic examination, repeated examinations with varying exposures were made.

The osteologic material which we have studied came from the edges and the immediate vicinity of typical mounds built by the "Mound Builders" in Crittenden and Mississippi Counties in the eastern part of Arkansas. It is definitely known that the present-day inhabitants of this area have never buried their dead near these mounds. The osseous remains were obtained from shallow graves which averaged about 18 to 24 inches in depth. In some graves there was evidence that the body had been inclosed in bark which formed a sort of coffin. For burial, the bodies were usually extended and placed on their backs. The heads were not pointed in any definite direction, say toward the West which is so definitely characteristic of burials by our present-day races. In addition to the osseous remains, the caches contained pottery, stone weapons and implements, beads, and other characteristic possessions. Not a single European trade object was found in any of the caches, refuse pits, or in the vicinity of the graves. The absence of these trade objects lends further support to the fact that these burials were made in precolonial times.

Anomalies. There were evidences of certain congenital anomalies. One femur of a young adult showed the characteristic difference in appearance of the proximal end which is seen in congenital dislocation of the hip joint. The dislocation in this case had occurred on the right side. The humeri of a young adult were of different sizes. The left humerus was 4 cm. longer than the right and appeared to be the normal of the two. The differences in size and length were probably the result of a poliomyelitis, a birth injury, or a congenital anomaly. There were examples of spina bifida of the lumbar and sacral vertebræ. There was one "steeple head" or oxycephalic

skull. Several skulls had been deformed by cradling or splinting during infancy.

Questionable Blood Dyscrasias. Two skulls had prominent parietal bosses which were heavy and thick (Fig. 1). The entire dome of each of these skulls had the appearance of coral. This appearance had resulted from the peeling away of the thinned, outer plate. The inner surfaces of these skulls were normal. The distal ends of the femurs of one of these skeletons were increased in diameter; the tibiæ had round, smooth anterior surfaces and were slightly increased in diameter (Fig. 2). Femurs and tibiæ of other skeletons revealed similar changes.

The foregoing lesions of the skull and long bones may be present in certain hemolytic anemias, and in sickle-cell anemia. The congenital hemolytic and erythroblastic anemias usually affect the children of races with dark skins. The recognition of the roentgenologic appearance of the changes in the craniums and long bones, which may be associated with certain blood dyscrasias, is a recent addition to our diagnostic procedures. Cooley, Witwer, and Lee,[2] in 1927, reported 7 cases of splenomegaly in which unusual changes occurred in the bones. All of the patients were children. Five of these cases had been previously reported in 1925. Baty, Blackfan, and Diamond,[1] in a study of erythroblastic anemia, added 20 cases to those already reported. In this latter study one finds a most detailed description of the roentgenologic changes occurring in the long bones in these hemolytic anemias. In 1924, according to Moore,[4] Graham reported the finding of changes in the long bones in a case of sickle-cell anemia, but there were no cranial alterations. However, since Graham's report, it has been a common observation that in sickle-cell anemia there may be alterations both in the long bones and in the cranium. Whipple and Bradford[6] do not believe that the pathologic changes observed in certain of these anemias are adaptive reactions to hyperplasia of marrow. They suggested that the abnormalities may be attributable in part to some metabolic disturbance on the order of abnormalities of bone in cases of scurvy or acromegaly. They concluded that all the abnormalities of these blood dyscrasias may be related to some racial or inherited defect. These remarks serve to illustrate that there are several groups of anemias which may produce skeletal and cranial changes.

In both sickle-cell and hemolytic anemia, the cranial vault may reveal an increased porosity of the cancellous portion of the bone. In the severe and later stage of the disease there may be thickening of the diploë to several times the normal. The outer table is thin and, during life, is not easily seen in the roentgenogram. In the dried specimen, the outer table may crumble away; such skulls may be described as possessing "increased porosity." The roentgenogram reveals the increased thickness and numerous fine stria-

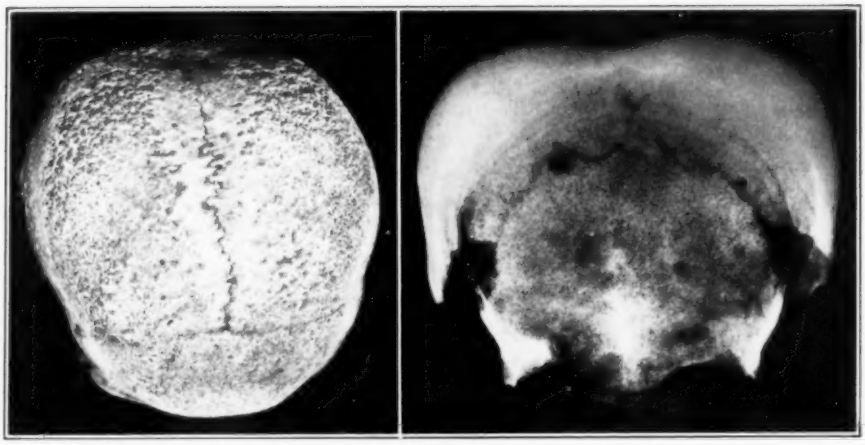

FIG. 1.—Gross and roentgenologic changes characteristic of certain anemias.

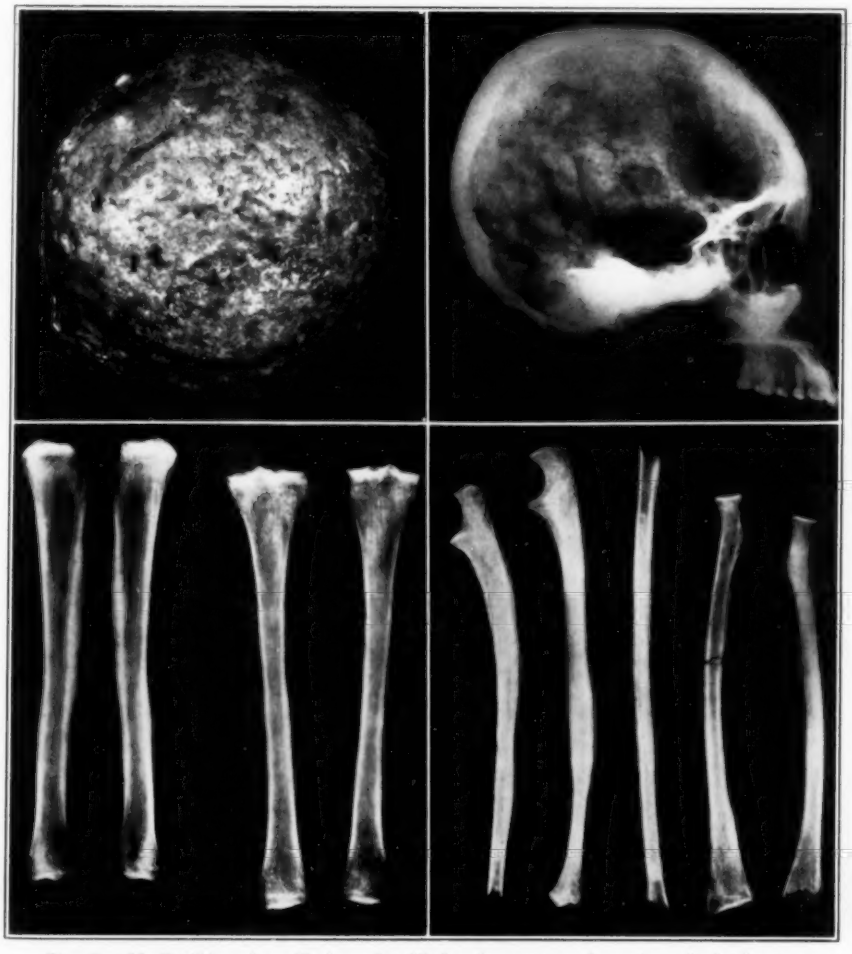

FIG. 3.—Skull, tibiæ, ulnæ, fibula and radii showing gross and roentgenologic changes characteristic of syphilis.

FIG. 2.—Long bones showing changes characteristic of certain anemias.

FIG. 4.—*a*, Tibia and fibula before sectioning; *b*, tibia after section; this bone shows irregular cortical thickening—so-called "blistering syphilis."

tions, so-called sun-bursts, which run perpendicularly to the tables of the skull. The long bones are wide because of an increase in the medullary portion. Rarefaction of the medullary portion results in a transparent appearance of the roentgenogram. There may be irregular trabeculations in the pelvis, vertebræ, ribs, clavicles and scapulæ.

It is a singular fact that these prehistoric American people should have had changes in their skulls and long bones, which are so suggestive of blood dyscrasias, such as erythroblastic, hemolytic, sickle-cell and other anemias. To those who have an interest in racial susceptibility and immunity to certain diseases, the presence of anemias which are peculiar to the Mediterranean races and Africans among "Mound Builders" tends to support the suggestion of Whipple and Bradford, namely, that these anemias are the result of some racial or inherited defect. That the "Mound Builders" may have had these anemias serves as further evidence that this race had a dark skin which is characteristic too of the American Indian. The morbidity of these blood dyscrasias among the "Mound Builders" will never be known, but it was not great. It probably was no greater than is the incidence of sickle-cell anemia among their colored "brethren," who at the present time tread the soil above their remains. Osseous changes, which are comparable to those described in this study, have been reported to have occurred among ancient Egyptians and ancient French people of the Gallo-Roman Period.[7] Moore made similar observations regarding ancient Peruvians.

Syphilis. There were lesions of the long bones, clavicles, skulls, and bones of the nose, which were similar to those of syphilis; the tibiæ often showed changes in the shafts. These changes, which were most prominent over the anterior surface of the middle third of the tibia were fusiform or oval in shape and shaded off rapidly toward the lower third, which was covered with muscle during life. Some tibiæ were greatly altered in appearance; the sharp anterior crest was replaced by a rounded surface and this thickening gave the shaft the appearance of having been bowed anteriorly. Fibulæ, radii, ulnæ, and clavicles showed similar changes, that is, a deforming osteitis and a low-grade osteomyelitis of varying degree.

In Table 1 we have tabulated the different bones of the same skeleton which showed lesions which may be characteristic of

TABLE 1.—THE NUMBER OF BONES WHICH REVEALED CHANGES CHARACTERISTIC OF SYPHILIS.

Skeleton	Tibiæ	Fibulæ	Radii	Ulnæ	Humeri	Crania
1	2	1				
2	1	..	1	1		
3	2	..	..	..	1	
4	2	2	2			
5	1	..	1			
6	2	1	2	2	..	1

syphilis. There were other isolated specimens which showed similar changes, but since no other part of the skeleton was thus affected they have not been enumerated.

The best evidence of osseous syphilis would be to find changes characteristic of this disease present in the tibiæ, fibulæ, radii, ulnae, and cranium of one skeleton. Such changes were found in one skeleton (Fig. 3) and are enumerated (Skeleton 6) in Table 1. Aside from this skeleton, we discovered other tibiæ, fibulæ, clavicles, which were the site of lesions suggesting lues, particularly gummata. In one skull the nasal bones as well as the bones of the roof of the mouth were eroded. In this case, in which the changes in the bones of the nose and hard palate were characteristic of syphilis, we have a fragmentary history. In the grave were deposited trinkets similar to those usually buried with children, and in no other grave of an adult was this custom observed. This suggests that possibly this person had the mentality of a child.

Syphilis of the skull may manifest itself in different ways; each lesion may produce a characteristic appearance and the signs of the various lesions may be present in the same skull. The gross appearance of a dried syphilitic skull therefore depends on the degree of the various predominating lesions. If periostitis with thickening was the predominating lesion, the skull would be increased in weight. The outer and inner surfaces of the calvarium may show various changes. Numerous abnormal vascular grooves and foramina indicate an increased blood supply, which is characteristic of early stages of syphilis of bone. The outer surface may present bony elevations which have a more or less convex surface, the so-called "tuberculated" form of syphilitic osteitis. Other syphilitic lesions of the cranium in most cases are localized, although extensive regions may be involved as a result of confluent foci. The skull of Skeleton 6 of Table 1 is an example of the "tuberculated" form of syphilitic osteitis.

The gross and the roentgenologic appearances of the foregoing specimens are in agreement that the changes were similar to those produced by syphilis. However, the possibility that these changes were artefacts, the result of the long time that the skeletons had remained in the ground, was considered. To obviate any such mistake, some of the specimens were sectioned. A tibia (from Skeleton 4, Table 1) was sectioned and photographed (Fig. 4). Further description of this specimen is not necessary, for it is rather characteristic of the so-called "blistering type" of syphilis of bone. More detailed sectioning of these bones for microscopic study was attempted but could not be done. Complete disintegration resulted from attempts at decalcification.

Syphilitic involvement of the bones of the body which are superficially situated is a chronic inflammatory process. The diagnosis of syphilis which is made solely on data obtained from the study of

skeletal material is always open to question, because there is no certain way of proving that the changes present were not the result of a chronic inflammatory process similar to that which may follow typhoid fever.

Operative Procedures. One skull, which may have been an example of trephining by means of a stone implement, was most interesting. This skull belonged to a normally developed adult man. It revealed an irregularity of the external surface of the left frontal bone, which involved only the external plate. In the upper part of the left parietal bone were 3 irregularly outlined perforations. The edges of these perforations were smooth and showed evidences of healing. There were no bordering areas of necrosis or evidences of fractures in this skull. The bone adjacent to these perforations was not thickened nor did it reveal any abnormal alterations. There was a healed fracture of the left clavicle of this skeleton.

The procedure of boring holes in the skull was practised extensively by certain races of ancient South Americans. They used flints shaped for boring or scraping to perform these operations. The motive for such a drastic procedure is not known. Authors with a kindly and humane feeling toward primitive people who practiced trephining have seen in it a surgical procedure, that is, a genuine desire to relieve suffering. Primitive people had highly developed instincts of self preservation. It would be difficult to imagine that a primitive person would submit to such a procedure after observing the terrific mortality which must have accompanied these "operations." Fractures which have been observed in other bones of the same skeletons might well be evidence that these unfortunate persons did not voluntarily submit to the "operation."

We are, however, fully aware of the fact that trephining was seldom, if ever, practised by the aborigines north of Mexico; therefore, this skull is presented as a probable example of this procedure. If it is not an example of trephining, the perforations in this skull probably were the result of some other traumatic agent which was followed by infection, erosion of the bones, and attempts to heal. There were many examples of the scraping of long bones. These operations were usually done on diseased bones and will be discussed in detail in another communication on this subject. The "Mound Builders" extracted teeth and reduced fractures.

Miscellaneous Lesions. A tibia, which belonged to a young adult, had an osteoma at the distal end. This tumor was of the congenital type. No lesions that seemed to fulfill the requirements of malignant growths were observed in any specimen.

Two healed fractures were found; one of these involved the right humerus and the other involved the left tibia. The fragments had healed in perfect alignment. There were two tibiæ which showed localized destruction of their cortices in the proximal thirds. These lesions were thought to be the result of puncture wounds, such as

might be inflicted by an arrow, or which might be the result of a Brodie's abscess. In each case a rather marked osteitis had been present in the region around the site of bone destruction for a long time.

The teeth that were still present were generally sound. There were a few perfect sets of teeth; however, positive statements concerning the dentures of this race cannot be made because so many of the teeth had fallen out after death. A decayed tooth does not withstand being buried for a long time and it does not withstand trauma incident to exhuming, or the subsequent drying. There were mandibles which showed evidence of marked dental infection and suppuration. Owing to the scarcity of stone, the corn was ground in wooden utensils; the meal, therefore, contained a minimal amount of grit to wear down and to destroy their teeth.

Hypertrophic changes about the borders of the lumbar vertebræ were occasionally observed. Hypertrophic changes were present about the knee joints in two skeletons. Three thoracic vertebræ were fused and bowed anteriorly in the very characteristic manner of spondylitis deformans. Fusion of the axis with the atlas was found in one skeleton.

There were no examples of an infectious type of arthritis or osseous tuberculosis. The presence of a lesion characteristic of tuberculosis would not be expected in bones which had been buried for so long a time. There were several examples of a severe, destructive osteomyelitis. One femur was of special interest since it was enlarged to twice its normal diameter and it was literally honeycombed in appearance, with numerous intracommunicating canals throughout its entire length.

Comment and Summary. As a rule, the skeletal remains of these people were well formed and well proportioned, which indicated that they had an excellent muscular system. Anterior bowing or lateral deformities of the bones of the legs, such as are seen in rickets, were not found. Irregular epiphyseal lines were not seen in any of the roentgenograms. The legs were straight, the pelves were narrow, and the arms were of moderate length. The heads were well formed if they had not been subjected to certain self-inflicted deforming procedures during their growth. In such cases the anteroposterior diameters were decreased and the bregmatic and lateral diameters were increased; these changes produced "flat heads." In some of these deformed heads there were symmetrical depressions above the orbits. One can be certain that the shape of these heads was not the result of disease but the result of cradling or moulding during growth.

Examples of the so-called "infectious arthritis" were not found. Hypertrophic changes about the margins of the knee joints and vertebræ were occasionally present. There were no changes characteristic of tuberculosis. An excellent example of spondylitis

deformans was present in three thoracic vertebræ. Osteomyelitis in extreme degrees was present in several specimens. The teeth were usually good. Healed tooth sockets indicated the antemortem extraction of teeth. Cauterizing or scraping of diseased long bones of the legs was a fairly common procedure. Fractures of long bones were set with a fair degree of precision.

The gross and roentgenologic presence of bony changes which may be seen in certain anemias were observed in the bones of the long extinct "Mound Builders" of Eastern Arkansas. One can be reasonably sure that when these lesions are present in the cranium and when they are accompanied by changes in the long bones that the individual had a blood dyscrasia. The diagnosis of syphilis among precolonial Americans who lived in Eastern Arkansas cannot be made absolutely. It is our opinion that sufficient evidence is present to say they had it. It is important to emphasize that the tibiæ and other long bones which were studied and described in this report were well preserved. We are entirely in accord with the findings of Williams[8] and of Means,[3] namely, that syphilis was endemic in North America before known contacts with Europeans. However, the findings recorded here are not presented as evidence of either the new or old world origin of syphilis.

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EXPERIMENTAL RADIUM POISONING.*

II. Changes in the Teeth of Rabbits Produced by Oral Administration of Radium Sulphate.

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In 1924, Theodore Blum,[1] a dentist, who was treating a painter of luminous watch dials for necrosis and osteomyelitis of the jaw bones, suggested that radium was the cause of this condition. This observation led to the investigations which established radium poisoning as an industrial hazard. In spite of the fact that it has

* This investigation has been made with the assistance of a grant from the Committee on Therapeutic Research, Council on Pharmacology and Chemistry, American Medical Association.

since been shown[2] that gingivitis, buccal infection, necrosis and osteomyelitis of the jaw are among the first symptoms to appear, no histologic studies of the teeth in the human cases or in experimental radium poisoning have been reported. Since the teeth are embedded in alveolar bone, which characteristically shows marked damage as a result of its radium content, and since they are similar to bone in composition, it would appear unlikely that the teeth and their supporting tissues could escape injury. The teeth are being bombarded constantly by emanations from the radium stored in the bony structures surrounding them and also, as will be shown, by radium actually deposited in the teeth structures.

The changes in the lymph nodes and bone marrow of rabbits who were given radium sulphate *per os* have been described in a previous communication.[4] These animals not only developed pathologic changes and a general symptomatology closely resembling that of radium poisoning as manifested in the human cases, but also showed marked pathologic disturbances in the teeth. The following report deals with a description of the changes in the teeth and their supporting tissues as noted in this series of rabbits.

To appreciate the pathologic processes discussed in this paper it might be helpful to review briefly the essential features of normal dentition in the rabbit.

The rabbit has 2 pairs of upper incisors. The large anterior upper incisors, which are much curved, show a well marked groove on their labial surface which extends from the apex to the cutting edge. This longitudinal groove gives the appearance of a channel whose walls slope acutely to meet in a sharp angle. Behind each of these teeth is a diminutive posterior incisor. The single pair of lower incisors are chisel-shaped and their roots extend far back into the jaws and also show the curve characteristic of an advanced rodent dentition. The cheek teeth, of which there are 12 maxillary and 10 mandibular, are all molariform. The columns of teeth are pressed together so that the anteroposterior diameter of each tooth is much less than the transverse. The lower molar teeth present on their occlusal surfaces three sharp grooves. These molar teeth articulate in such a manner that every lower tooth opposes 2 upper teeth; the first and last teeth of the upper jaw, however, have each only 1 opposing tooth. The incisors, as well as the cheek teeth, grow from persistent pulps and are therefore never shed. The rate of growth of the incisor teeth is from 2 to 3 mm. per week throughout the life of the animal (Orban[3]), but the growth of new dentine is balanced by a constant wearing down process (attrition), so that the teeth remain at a constant length. The investment of enamel in the incisor teeth, instead of being continued around the whole circumference of the tooth, is confined to the anterior and lateral surfaces, on the former of which it is thickest; the posterior surface is covered by a layer of primary cementum. The enamel organ, however, completely surrounds the apex of the roots.

Histologically, the dentine forms the greater portion of the entire tooth. Two layers of dentine can be distinguished, one of which is a wide layer showing a more or less rhythmic and uniform stratification, with occasional shallow undulations. This is the layer which borders the pulp cavity. An outer, narrower layer consists of granules which gradually increase in size as they approach the periphery, where they coalesce into quite large "globules of calcification." As the dentine is followed towards the root the inner, stratified layer gradually decreases in width until it finally disappears, while the outer, granular layer, which is here considerably coarser, tapers to the apex.*

Material and Method. Four rabbits 6 months of age were used, of which 2 were males, each weighing 2700 gm. and 2 females, each weighing 1800 gm. The animals were kept on a normal and adequate standard diet throughout the experiment. Each animal was fed several drops of a suspension of radium sulphate in glycerin by medicine dropper 3 times daily for a period of 90 consecutive days. By the end of this period, each rabbit had received orally about 100 micrograms of radium sulphate. Glycerin was found to be a suitable vehicle and the animals seemed to enjoy the sweet taste, thus insuring ingestion of most of the radium salts. The rabbits were observed daily for physical changes, and blood studies were made biweekly. The animals survived for 3, 12, 13 and 18 months, respectively, after the cessation of radium administration.

Gross Changes of Teeth. For the first 2 months of the radium administration the teeth showed no abnormal changes. During the third months, however, the lower incisor teeth of all showed a brown mottling. In the next few weeks the mottling became more marked and similar discolorations gradually appeared on the other teeth. The entire length of the extraälveolar portion of the incisor teeth showed, on the labial and lateral aspects, a transverse corrugation which was characterized by ridges, unevenly spaced and varying in thickness and height. The longitudinal groove on the labial surface of the upper incisor became shallower and more rounded. At this time, and associated with these dental changes, there was a gingivitis, and in manipulating the jaws there was manifested a progressive tenderness. Soon after the cessation of radium administration, a gradual abrasion of the lower incisor teeth became evident and this continued, until, in the animal which survived the longest (18 months) the lower incisors became worn down to the gum margin. The upper incisors showed to a lesser degree the same changes, the sharp incisive edges being worn off (abraded) with the formation of broad occluding surfaces.

The upper and lower molar teeth also showed striking gross changes. They were irregularly abraded, some being worn down to the gum margin. Some presented a single, flattened, oblique sur-

* For a more detailed description of the histology of rabbits' teeth the reader is referred to the article by Orban.[3]

face, while others were sharp, ragged and irregular. Small, oval and rounded pits were found on the lateral surfaces of the teeth. Irregular masses of bone had grown in between the teeth (Fig. 2) and produced a solid junction (ankylosis).

In the meantime, the animals developed abscesses of the jaw, and Roentgen ray examination revealed irregular areas of rarefaction of the mandibular plates. When representative teeth were placed on extremely rapid, dry, photographic plates (Standard Orthonon, 4.5 by 6 cm.) for 6 days, definite shadows (autophotographs) corresponding to the shape of the various teeth were produced, indicating the presence of radium within the tooth. Normal rabbit teeth treated in the same manner produced no changes on the photographic plates (Fig. 3).

Histologic Changes. Striking abnormalities were found in all structures of the teeth, in the periodontium and in the adjacent bone (Fig. 1A). (Compare with Fig. 1B.) The dentine showed evidence of disturbed calcification. In place of the normal, rhythmic stratification of the dentine, one found an irregularity in the spacing of the calcified and uncalcified layers. These incremental lines were sometimes localized in fan-shaped areas (Fig. 4) without any definite relationship to the pulp cavity. Not only was there disturbance of the normal architecture, but there was also an excessive deposition of calcium in many of the incremental lines. The globules of calcification were very large and their union was incomplete, resulting in an increase in the number and size of the interglobular spaces. There were also irregular zones of uncalcified or poorly calcified matrix, which frequently presented a porous or cystic appearance. Thus, zones of very poorly calcified or completely uncalcified dentine were found irregularly distributed, or alternating with areas of excessive calcification, and without any definite relationship to the pulp cavity. Certain areas in the dentine revealed a decreased number of irregular tubules, which were widely spaced.

The intraälveolar portions of the teeth were irregular serrated as a result of deeply excavated areas of resorption of dentine, which were frequently filled by a proliferating fibroblastic tissue extending from the periodontium. Similar spaces, filled with the same type of proliferating fibroblastic tissue, were found in the center of the dentine structure, giving the appearance of internal areas of resorption. Serial sections showed that the so-called internal areas of resorption communicated with the excavated areas on the surface of the tooth. These excavated areas were frequently lined by a deposition of cementum. The cementum in places was of the primary variety, consisting of a fine fibrillar structure, whereas in other places it was of the secondary variety, consisting of cells embedded in a matrix and resembling bone. In certain areas, especially around the roots, the secondary cementum showed a multilaminated

FIG. 1A.—A cross section of molar tooth showing deeply excavated areas of resorption of dentine (R), filled with proliferating fibroblastic tissue and small spicules of newly formed bone (S). Resorption of alveolar bone (A). Heavy deposition of cementum (M). Resorption of intradental bony septum with fibroblastic tissue replacement (B). Acellular alveolar bone marrow (D).

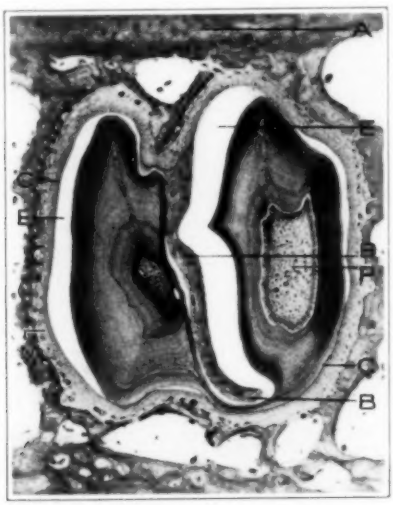

FIG. 1B.—Cross section of lower molar tooth of normal rabbit (after Orban) alveolar bone (A). Enamel space (E). Intradental bony septum (B). Pulp (P). Cementum (C). Periodontal membrane (M).

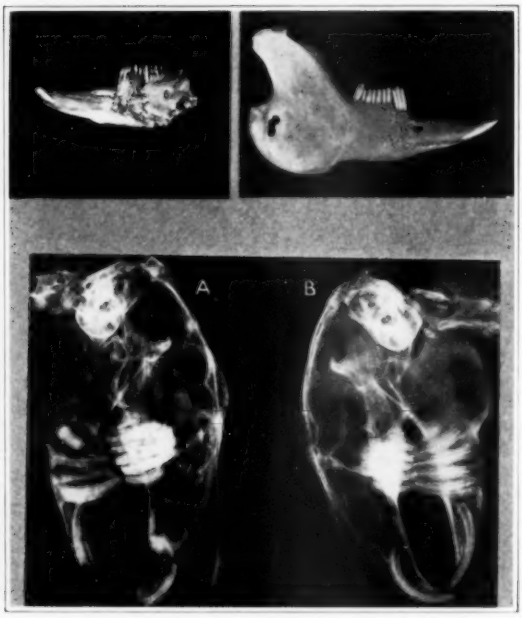

FIG. 2.—Upper.—Ingrowth of bone between molar teeth, and abrasion of the incisor tooth. Due to its fragility, caused by the osteoporosis, the mandibular plate was separated in the process of preparation. Note the appearance of the normal mandible at the right.
FIG. 2.—Lower.—Note the striking changes in the molar and incisor teeth of the radium-fed rabbit (A) as compared with the normal control rabbit (B).

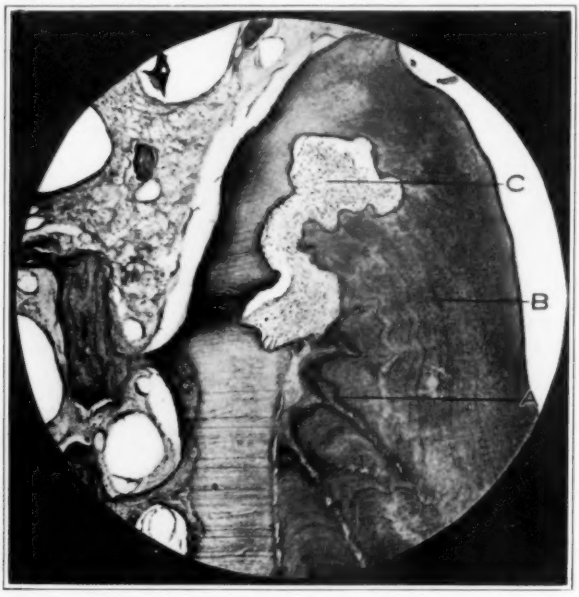

FIG. 4.—Incramental lines (A) localized in fan-shaped areas and large globules (B) of calcification of dentine. Internal area of resorption (C).

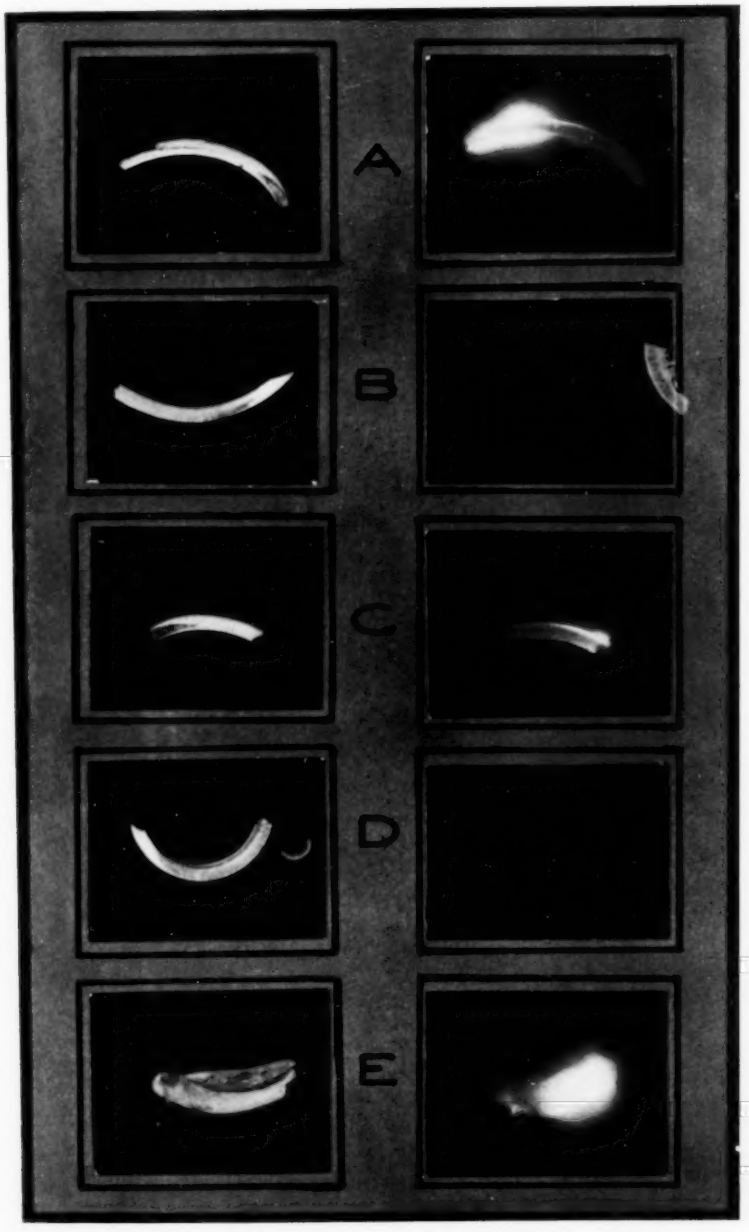

FIG. 3.—Photographs and corresponding autophotographs of teeth of radium-treated rabbits. Teeth B and D were from normal (control) animals and produced no autophotographic shadows.

FIG. 5.—A large spicule of dentine (A) containing large globules of calcification, surrounded by fibroblastic proliferation (B). Surface of resorbed tooth lined by hyperplastic layer of secondary cementum (C). Small epithelial-lined cyst in periodontal membrane.

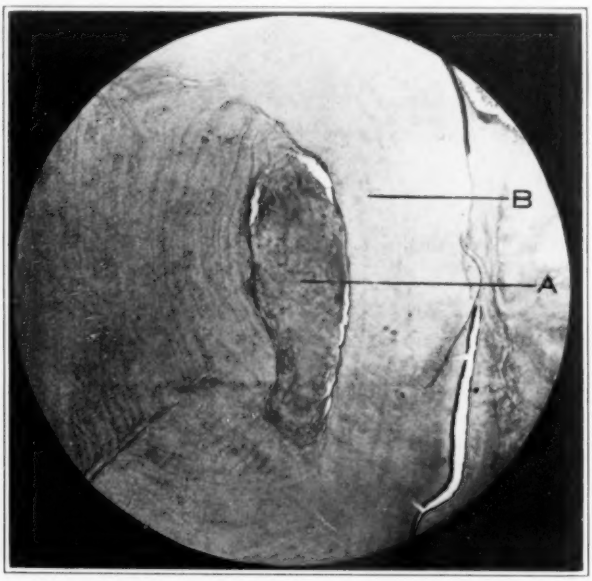

FIG. 7.—Pulp chamber filled with secondary dentine (A) and separated from the primary dentine (B) by a zone of darker staining undifferentiated dentine.

FIG. 6. Large mass of newly formed bone (A) forming a solid junction with the tooth. Note the external and internal areas of resorption (B).

FIG. 8.—Extensive proliferation of atypical epithelial cells (A) about the apex of a molar tooth. Note the globular, calcified masses (B).

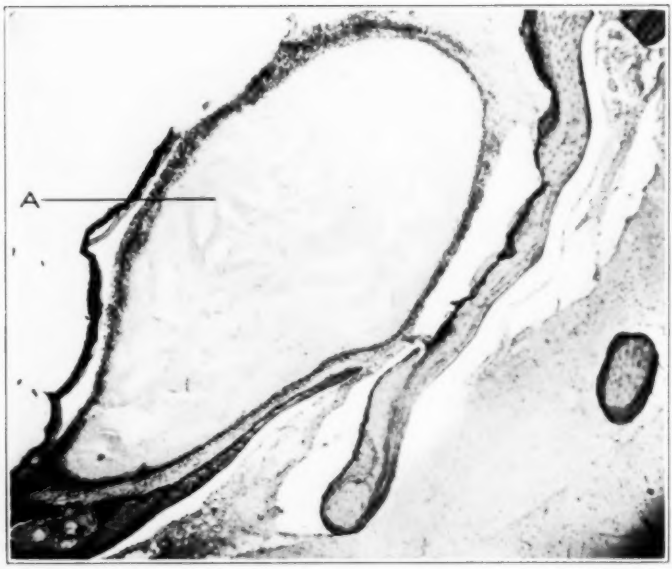

FIG. 9.—An epithelial lined cyst containing cholesterol crystal spaces (A) in the periodontal membrane.

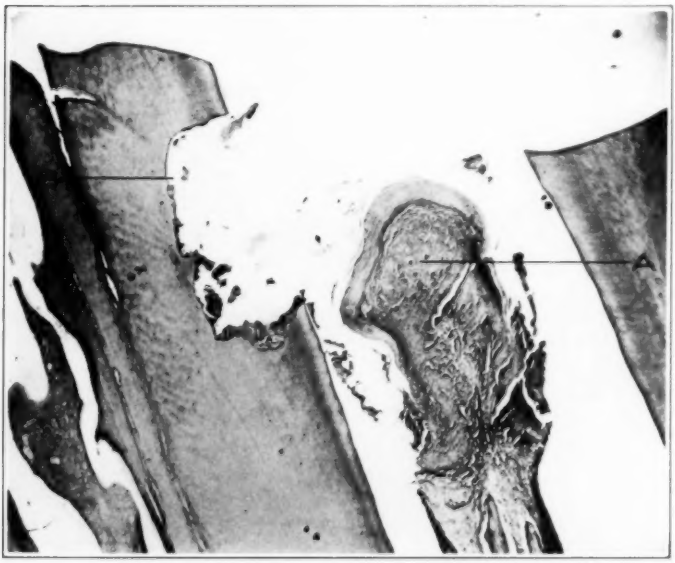

FIG. 10.—Hypertrophy of the interdental papillæ (A) (hypertrophic gingivitis) adjacent to an area of resorption (B).

structure indicating a marked hyperplasia. The cementum cells in the superficial layers appeared normal, but in the deeper layers near the dentine the cells had completely degenerated and the lacunæ were empty. At times, a layer of primary cementum was found to alternate with a layer of secondary cementum; in other instances, fragments of fractured dentine were found to be reunited by an ingrowth of excessively calcified cementum. The fibroblasts of the peridontal membrane showed extensive proliferation. The cells were arranged in irregular, coursing bands and the nuclei showed numerous mitotic figures. In places, this tissue was infiltrated by a few lymphocytes and plasma cells. It showed but slight vascularity and contained no giant cells. It showed also occasional, globular, calcified bodies with concentric laminations (cementicles). As stated above, this hyperplastic tissue not only invaded the tooth structure but also extended into the marrow spaces of the surrounding bone. The bone of the alveolar processes had been extensively replaced by large, irregular masses of newly formed bony trabeculæ and presented a compact structure wherein the lacunæ were closely set and the marrow spaces smaller than in the corresponding sections from control animals. Large, irregularly shaped masses of this uniform bone were frequently found attached to the teeth by secondary cementum, producing solid junctions (ankylosis) between bone and the resorbing teeth (Fig. 6). In some sections almost the entire intraälveolar portions of the teeth were found to be resorbed and replaced by newly formed bone, which was also focally united to tooth structures. It was observed that the dentine bordering the pulp cavity showed no areas of resorption. This observation is similar to that of J. Tomes on the resorption of deciduous teeth.[5]

Fractures of the dentine involving the calcified areas were occasionally encountered. Irregular spicules of dentine, varying in size and showing large globules of calcification, were found completely separated from the tooth and surrounded by proliferated fibroblastic tissue (Fig. 5). Osteoclasts were not found along the borders of the resorbing dentine nor in the vicinity of the sequestrated pieces of dentine; in fact, only a few of these cells were found near the resorbing alveolar bone. The bone marrow of the alveolar processes was almost completely acellular and presented a myxomatous appearance. The arterioles, in many places, showed varying degrees of intimal proliferation; occasionally, they even presented complete obliteration of the lumen. The media showed degenerative changes and small areas of necrosis.

No normal pulp tissue was found in any of the sections. The pulp chambers were completely or partially filled with secondary dentine which showed a scant number of irregular dentinal tubules. Between this irregular secondary dentine and the surrounding layer of primary dentine there was a transitional zone consisting of

darker staining, more compact, undifferentiated dentine (Fig. 7). Only rarely were any cellular elements found in the pulp chamber and these usually consisted of fibroblasts and occasional blood-vessels. Where secondary cementum was found in the pulp chambers it was located near the roots, apparently representing an ingrowth from without.

Frequently the enamel organ showed various stages of degeneration, including complete necrosis. The ameloblasts, normally present as a single layer of tall, regularly arranged columnar cells with basally placed nuclei, showed various degrees of flattening; in some areas they appeared as low cuboidal cells with centrally placed nuclei, while in other areas there was marked atrophy or complete disappearance of this layer. The epithelial cells of the stratum intermedium showed hyperplastic changes, as evidenced by the widening of this layer and the presence of more numerous mitotic figures than are normally seen. The cells of the stellate reticulum showed necrosis as evidenced by the fading of their nuclei and the loss of their cellular outlines. About the apices there was an extensive proliferation of atypical epithelial cells. These cells, at times, bore a resemblance to those of the stratum intermedium and were arranged in streaming strands or in concentric whorls. Intermigled with these cells were cells resembling those of the stellate reticulum, the latter being in various stages of degeneration (Fig. 8). In some instances there were small, isolated, irregularly shaped areas of necrosis, in which the cellular details were completely lost and vacuolization was pronounced. Occasionally, globular, calcified masses, presenting a concentrically laminated appearance, were found in this hyperplastic tissue. Although the above description strongly suggests that these areas arose from the enamel organ, it is also possible that they had their origin in the epithelial rests normally present in the periodontal membrane.

A conspicuous feature of many of the sections was the presence of cysts, obviously arising in the periodontal membrane. These structures were lined by a broad layer of stratified squamous epithelium and contained desquamated epithelial cells, albuminous fluid, and cholesterol crystal spaces. The manner of their development was suggested by the finding of areas of necrosis and small cystic spaces in the center of rounded masses of proliferated epithelial cells, which probably had their origin in the aforementioned epithelial rests of the periodontal membrane. The abscesses of the jaws found during life were considered to have arisen through infection of certain of these radicular cysts (Fig. 9).

The gingival tissue also showed proliferative and degenerative changes. Not infrequently, small nodular protrusions, originating from the interdental papillæ, were seen. These were most frequently found near or protruding into excavated portions of the

teeth. They were covered by a layer of hornified, hyperplastic, epithelial cells and the subepithelial tissue was fibrous and poorly vascularized. In histologic appearance, they resembled papillomas (hypertrophic gingivitis) (Fig. 10).

Summary. Observations on animals given radium sulphate *per os* show that the radium is stored not only in the alveolar bone of the jaw but also in the teeth themselves, producing a pronounced alteration of the entire morphologic picture of the tooth.

There is a marked disturbance in calcification, with resorption of teeth and the formation of ankylosis by the ingrowth of newly formed bone, which also replaces the absorbed bone of the alveolar process. The essential changes in the enamel organ consist of flattening and atrophy of the ameloblasts, with hyperplasia of the stratum intermedium and subsequent degeneration and necrosis of the entire formative structure. The normal pulp tissue is replaced by abnormal, irregular secondary dentine masses. The surrounding periodontium shows an extreme hyperplasia of fibroblastic tissue, with invasion of surrounding structures. The development of cysts arising from epithelial rests in this membrane is also an interesting finding.

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THE GASTRIC ACIDITY IN ALCOHOL ADDICTS.

With Observations on the Relation of the B Vitamins to Achlorhydria.

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Alcohol is an agent alleged to impair gastric secretion. As early as 1880 Fenwick[6] stated that the prolonged excessive use of alcohol caused injury to the gastric mucosa with subsequent lack of secretion. Some 25 years later Faber and Lange,[5] on the basis of pathologic studies, stressed alcohol as an exogenous cause of "gastritis" and the accompanying anacidity. As recently as 1926 Faber[4]

again emphasized this view. Merritt and Moore[14] in 1930 reported the gastric analyses as normal in 7 of 8 alcohol addicts. Minot, Strauss and Cobb[15] studied by fractional analysis the gastric secretion of 43 patients with "alcoholic" polyneuritis, using either the Ewald or the alcohol test meal, but administering histamine to only half of their subjects showing achlorhydria. By these methods they found the incidence of achlorhydria to be 50%, hypochlorhydria 33% and adequate free acidity 17%. The expected normal incidence of achlorhydria in their subjects was 12%. As they were unable to find significant statistical data concerning the state of the gastric secretion in alcohol addiction, these authors could not conclude whether the increased incidence of achlorhydria and hypochlorhydria was characteristic of "alcoholic" polyneuritis or merely of chronic alcoholism.

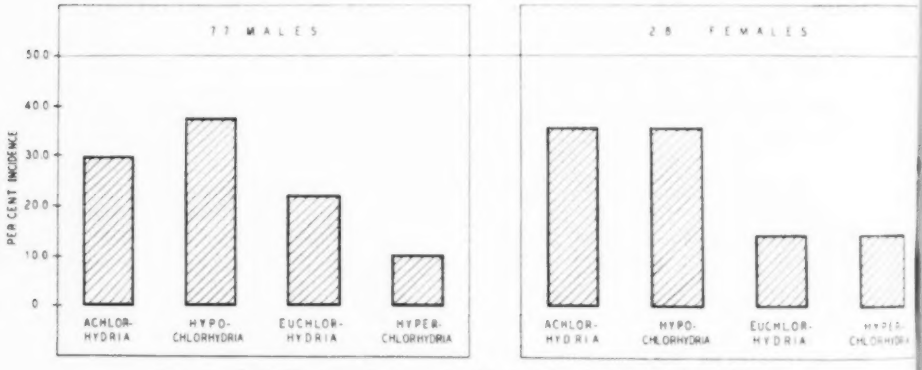


FIG. 1.—Distribution of types of acid secretion in 105 alcohol addicts.

In order to obtain significant data concerning the state of the gastric acidity in chronic alcoholism, we have studied the gastric acidity curves of 105 alcohol addicts, of whom 77 were males and 28 were females. These subjects used alcohol in large quantities over periods ranging from months to years, either daily or periodically. The method of conducting the test was that advocated by Bloomfield and Polland.[2] The alcohol test meal was used, and histamine given if free acid was absent in the first three samples. The gastric analyses reported in this paper were obtained as a rule between the third and seventh day of hospitalization.

The criteria established by Vanzant and associates[19] are used to classify these subjects into four groups according to the maximum degree of free acid found. Achlorhydria is the complete absence of free acid after the administration of histamine. Hypochlorhydria includes free acid values from 1 to 29 units in males and 1 to 19 units in females. Euchlorhydria, or normal values, ranges from 30 to 59 units of free acid in males and 20 to 49 units in females. Hyper-

chlorhydria includes free acid values of over 59 units in males and of over 49 units in females.

Liver function studies were conducted on these patients by methods reported in a previous study on catarrhal jaundice.[10] Since the degree of bromsulphalein retention[16] at the end of 30 minutes seemed in general to parallel the degree of liver dysfunction as measured by the other tests, we are reporting in this paper only the results of this test. A complete hematologic status was determined at weekly intervals on each of these patients. Haden's[8] methods and criteria, corrected for our laboratory, were used on patients examined prior to September, 1935. Since then Wintrobe's[21] methods and criteria have been used.

RESULTS. The distribution of the types of acid secretion obtained in our 105 patients is presented in Figure 1. Adequate secretion (euchlorhydria and hyperchlorhydria) of free acid occurred in 32% of the 77 male subjects and in 29% of the 28 female subjects. Inadequate secretion (achlorhydria and hypochlorhydria) of free acid was found in 68% of the male subjects and in 71% of the female subjects. Achlorhydria occurred in 30% of the males and 35% of the females, while hypochlorhydria was found in an additional 38% of the males and 36% of the females. In Table 1 we have

TABLE 1.—AGE AND SEX DISTRIBUTION OF ACHLORHYDRIA IN 105 ALCOHOL ADDICTS.

Ages.	Males.				Females.			
		Anacidity.				Anacidity.		
	Total cases.	Total cases.	Per cent frequency.	Per cent normal expected frequency.	Total cases.	Total cases.	Per cent frequency.	Per cent normal expected frequency.
20–29	2	0	0	2.90	5	0	0	4.70
30–39	20	8	40.0	3.50	8	1	12.5	7.50
40–49	30	8	26.6	10.00	9	5	55.5	19.10
50–59	21	6	28.5	13.90	4	3	75.0	18.00
60–69	4	1	25.0	31.70	2	1	50.0	21.90
Totals	77	23	29.9	10.28	28	10	35.7	13.25

tabulated the incidence of achlorhydria in our subjects according to age and sex, and in Figure 2 we have compared these findings with the expected frequency in a group of normal individuals from the data of Bloomfield and Polland.[2] In each age group in both male and female subjects between the ages of 30 and 59 the frequency of achlorhydria exceeded the expected normal incidence. In the male groups between 30 and 59 years of age there are sufficient cases for the results to be significant. In the female groups the number of cases is small, but since the results parallel the findings in the male groups they, too, are probably significant.

Pellagra was present in 27 (26%) of our subjects, all but 5 of whom had in addition a polyneuritis. Adequate secretion of free acid occurred in 11%, hypochlorhydria in 37%, and achlorhydria in 52% of the subjects in this group. The incidence of achlorhydria in this group is about the median of that reported by various workers[9] in endemic pellagra.

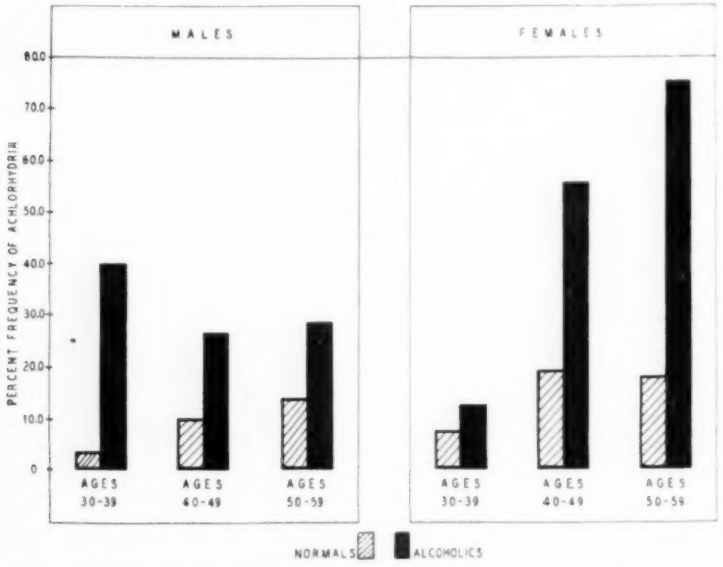


FIG. 2.—Age and sex distribution of achlorhydria in alcohol addicts and normal subjects.

Polyneuritis was present in 74 (70%) of our subjects, 22 of whom also had pellagra. Since the gastric acidity of the pellagrins has been noted separately, we have included in this group only the 52 subjects without pellagra. Adequate secretion of free acid occurred in 29%, hypochlorhydria in 42%, and achlorhydria in 29% of the subjects in this group. Our incidence of achlorhydria in this polyneuritic group without pellagra is smaller than the 50% reported by Minot, Strauss and Cobb.[15] This difference can be largely explained by the facts that they used histamine to stimulate gastric secretion in only one-half of their cases showing achlorhydria, and that 14 subjects having pellagra were included in their polyneuritic group.

Our 26 subjects who did not have pellagra or polyneuritis are included in an "uncomplicated" group. Adequate secretion of free acid occurred in 58%, hypochlorhydria in 27% and achlorhydria in 15% of these subjects. The expected frequency of achlorhydria in a group of normal subjects of the same age and sex distribution

would be about 12%. The difference of 3% is probably not significant. In this group of 26 "uncomplicated" alcohol addicts, 16 gave reliable histories from which the VIT/CAL ratios[3b] could be estimated, which permitted us[11] to estimate quantitatively the adequacy of their diets in respect to vitamin B. These subjects, as pointed out by Jolliffe, Colbert and Joffe,[11] failed to develop polyneuritis either because their vitamin B intake was adequate or because of the short duration of the deficiency. In this group of 16 subjects without clinical evidence of vitamin B deficiency, only 1 subject had achlorhydria, 1 had hypochlorhydria, and the remaining 14 yielded adequate acid values. This result is no different than one would expect in a group of normal subjects of the same age and sex distribution.

Quantitative anemia occurred in 80% of our 105 subjects. The red cells of all subjects, however, are classified as normocytic, microcytic, or macrocytic as determined by the volume index or the mean corpuscular volume. Normocytosis was present in 36%, microcytosis in 26% and macrocytosis in 36% of the subjects. Achlorhydria occurred in 40% of the normocytic group, in 38% of the microcytic group and in only 20% of the macrocytic group. In the subjects having achlorhydria, normocytosis occurred in 45%, microcytosis in 31% and macrocytosis in only 24%.

Correlation of the liver function tests with the gastric acidity is especially important in view of the high incidence of achlorhydria in liver disease. As a group those deficient in acid secretion showed a slightly greater impairment of liver function, as measured by the tests used, than did those with adequate acid secretion. In the acid deficient group the average of the initial bromsulphalein retention was 28.5 ± 12.6 as compared with 21.5 ± 12.7 in the acid adequate group. In view of this large probable error in each group the difference is not statistically significant. Because of the marked difference in incidence of achlorhydria in the pellagrins, the polyneuritics, and in the "uncomplicated" group, we have compared the degree of liver dysfunction in these three groups, irrespective of the state of the gastric acidity. The average initial bromsulphalein retention in the pellagrins was 37.5 ± 14.9, in the polyneuritics 24.1 ± 12.1, and in the "uncomplicated" group 22.1 ± 11.3. The results in the polyneuritic and "uncomplicated" groups are practically identical. In view of the size of the probable error, the greater retention of bromsulphalein in the pellagrins over that of the other two groups is probably not significant. These results may represent only the inadequacy of our methods of testing the functions of the liver.

Discussion. The study of the gastric acidity in this group of 105 alcohol addicts during the latter half of the first week of hospitalization showed achlorhydria in about one-third of all subjects, with another one-third showing hypochlorhydria and one-third show-

ing adequate secretion of free acid. The expected frequency of achlorhydria in a normal group of the same age and sex distribution as calculated from the data of Bloomfield and Polland[2] would be about 11%. The frequency of achlorhydria in this group of alcohol addicts is, therefore, about 3 times the expected normal. Is this high incidence of achlorhydria due to the direct effect of alcohol *per se?* Is it due to or merely associated with the dietary deficiency causing polyneuritis or pellagra? Is it due to or associated with the macrocytic anemia or the liver disease? We have shown that there is no evidence relating it to macrocytic anemia or liver disease in our subjects. We believe that it is not due to alcohol *per se;* that it is associated with polyneuritis but is not due to vitamin B deficiency; also, that it is associated with pellagra but not definitely due to a lack of the pellagra preventive factor.

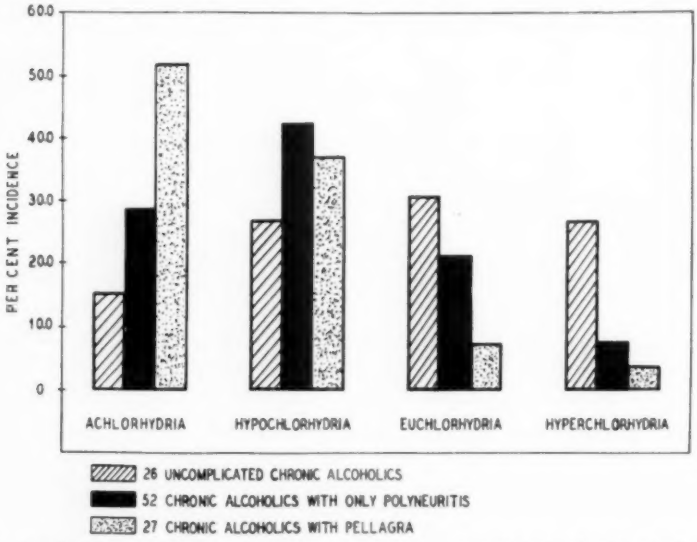
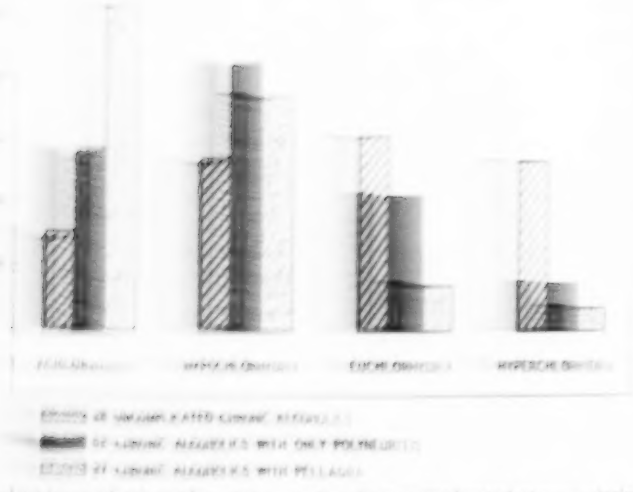


FIG. 3.—Incidence of types of gastric secretion in uncomplicated chronic alcoholics and in those having polyneuritis or pellagra.

In support of these contentions we present the following evidence. Achlorhydria occurred in 52% of the pellagrins, in 29% of the polyneuritics, and in 15% of the "uncomplicated" group (Fig. 3). The duration of the immediate bout of alcoholism in the above three groups, though there are exceptions, can be roughly estimated as follows: months to years in the pellagrins, weeks to months in the polyneuritics, and days to weeks in the "uncomplicated" group. The incidence of achlorhydria, therefore, seems to vary directly with the duration of the alcoholism. Evidence, however, that this assumption is not valid is furnished by a critical analysis of our data. It is true that the entire "uncomplicated" group had

an average *per diem* intake of alcohol less than the average of the polyneuritic group. Nevertheless, many of these subjects drank a sufficient quantity of whiskey over an effective period of time to cause achlorhydria if alcohol *per se* were its cause. To illustrate this point, 9 of the 16 "uncomplicated" subjects giving adequate histories[14] used from 8 to 24 ounces of whiskey daily for periods varying from 6 months to 40 years. The average maximum free acidity in this group was 40 units, with histamine stimulation required in but 1 subject. In the 24 subjects with polyneuritis who gave adequate histories,[14] 11 subjects used 8 to 24 ounces of whiskey daily for periods varying from 6 months to 25 years. The average maximum free acidity in this group was 25 units, but histamine stimulation was required in 8 subjects. Prior to the administration of histamine the free acidity averaged only 7 units. The relative necessity of administering histamine in these two groups indicates the relative incidence of anacidity without stimulation by this drug, and suggests that the difference of maximum free acidity in the two groups is significant. Since the group showing a normal incidence of achlorhydria used as much whiskey and over as long a period of time as the group showing a high incidence of achlorhydria, we believe that alcohol *per se* is not the cause of achlorhydria in the alcohol addict.

The 26 "uncomplicated" subjects did not have polyneuritis because, as shown by Jolliffe, Colbert and Joffe,[11] either an adequate intake of vitamin B was maintained or the duration of the deficiency was very brief. Of the 16 subjects in this group whose VIT/CAL ratios could be estimated quantitatively,[11] only 1 subject (417) had achlorhydria, 1 (325) showed hypochlorhydria, and the remaining 14 subjects showed adequate acid secretion. In our group of 52 alcohol addicts with polyneuritis we were able to estimate quantitatively the VIT/CAL ratios of 24. As measured by this ratio, each of these 24 subjects had a vitamin B intake below his predicted requirement over a period of time adequate to produce polyneuritis.[11] Achlorhydria occurred in 7 of these (Subjects 258, 300, 327, 336, 388, 392 and 468), an incidence of 29%, which is identical with the incidence found in the entire polyneuritic group of 52 subjects. From the fact that achlorhydria is relatively common in alcohol addicts with proven vitamin B deficiency and of but normal frequency in alcohol addicts without vitamin B deficiency, it would appear that vitamin B is an achlorhydria preventive factor. This evidence is, however, not conclusive, as the achlorhydria preventive factor may be a separate entity frequently inadequate in American diets when vitamin B is also inadequate. In support of the conjecture that the achlorhydria preventive factor and vitamin B are not the same fraction of the vitamin B complex we have the work of Kitamura and Shimazono[13] and Keefer,[12] who show that achlorhydria is not associated with beriberi, the classic clinical picture of vitamin B



In support of these contentions we present the following evidence. Achlorhydria occurred in 97% of the pellagrins, in 29% of the polyneuritics and in 15% of the "uncomplicated" group (Fig. 3). The duration of the immediate bout of alcoholism in the above three groups, though there are exceptions, can be roughly estimated as follows: months to years in the pellagrins, weeks to months in the polyneuritics, and days to weeks in the "uncomplicated" group. The incidence of achlorhydria, therefore, seems to vary directly with the duration of the alcoholism. Evidence, however, that this assumption is not valid is furnished by a critical analysis of our data. It is true that the entire "uncomplicated" group had

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deficiency. Additional evidence that vitamin B and the achlorhydria preventive factor are not identical may be inferred from the gastric acidity of the 5 subjects in this study who had pellagra without polyneuritis. Cowgill[3b] used the presence or absence of polyneuritis as the criterion of the adequacy or inadequacy of a diet in the determination of the vitamin B requirement of man. These 5 subjects, on this basis, were not vitamin B deficient. Achlorhydria, however, was present in 4 of these 5 subjects, while the fifth showed hypochlorhydria. In endemic pellagra achlorhydria occurs in about 35 to 90% of the subjects;[9] if these pellagrins consumed a diet similar to Goldberger's[7] or the traditional diet of Southern pellagrins, consisting of salt pork, corn, and molasses, they would presumably have an adequate vitamin B intake.[3b] In endemic pellagra, therefore, vitamin B in amounts sufficient to prevent the development of polyneuritis does not prevent the development of achlorhydria. This suggests that the achlorhydria preventive factor and the pellagra preventive factor are frequently associated, or they may be the same fraction of the vitamin B complex. But how would a deficiency in the pellagra preventive factor cause achlorhydria in a subject with polyneuritis uncomplicated by clinical pellagra? In our experience the alcohol addict with polyneuritis usually consumes a diet qualitatively inadequate in the entire vitamin B complex as well as in vitamin B. The failure of most subjects to develop pellagra can be attributed to the fact that vitamin B deficiency manifests itself by polyneuritis in from 7 to 21 days of estimated absolute deficiency,[11] while clinical evidence of deficiency in the pellagra preventive factor requires a relatively longer period of time to become manifest. If the vitamin B deficiency, that is polyneuritis, does not result in the restriction of alcohol and the resumption of an adequate diet, clinical pellagra may still not develop unless the patient is exposed to a dermatitic exciting factor present in sunlight. It is possible therefore that a lack of the pellagra preventive factor causes achlorhydria even though clinical pellagra may not exist. Cowgill,[3a] however, was unable to impair gastric secretion in dogs by means of the Goldberger diet. In view of the recent work of Ruffin[17] and Smith and Spies[18] it would be interesting to note the effect of sunlight on the gastric secretion of these animals. Cowgill[3a] was able, however, to impair gastric secretion by feeding a diet inadequate in the entire vitamin B complex, and to cause a return of gastric secretion by the addition of Vitavose to the diet. From these experiments Cowgill inferred that vitamin B was necessary to maintain adequate gastric secretion. Vitavose, however, contains in addition to vitamin B other fractions of the vitamin B complex, and this conclusion is not necessarily valid. In this connection Webster and Armour[20] show that autoclaved yeast, in which the vitamin B is presumably destroyed, is effective in restoring normal gastric secretion in ani-

mals on a vitamin B complex deficient diet, though not as effective as non-autoclaved yeast. They also note that vitamins A, D or C apparently play no rôle in the maintenance of normal gastric secretion.

From the entire line of reasoning here presented it seems to us that an achlorhydria preventive factor is contained in the vitamin B complex. It is probably not the heat labile antineuritic vitamin B fraction. It is closely associated with the heat stable antidermatic pellagra preventive fraction. In view of the facts that achlorhydria is not constantly associated with pellagra and that vitamin G is now thought to consist of several fractions such as the pellagra preventive factor, the antiblack tongue factor, lacto-flavin, and vitamin B_6,[1] it seems probable that the achlorhydria preventive factor and the pellagra preventive factor are not identical. If this latter conjecture is true, one may speculate that this achlorhydria preventive factor is partially heat labile; that it is present in adequate amounts in the diet of Chinese who develop beriberi, but is frequently inadequate in the diet of alcohol addicts who develop polyneuritis or pellagra. It may be suggested therefore, in order to prevent achlorhydria, that the chronic alcohol addict who will not or cannot resume normal drinking habits should supplement his diet with a rich source of the vitamin B complex.

Summary and Conclusions. We have studied by uniform methods the gastric acidity curves of 105 chronic alcohol addicts. Whereas the expected incidence of achlorhydria in a normal group of the same age and sex distribution would be 11%, in this alcoholic group achlorhydria occurred in 33%. Dividing the subjects into three subgroups as follows: the "uncomplicated" subjects, the polyneuritics and the pellagrins, achlorhydria occurred in 15, 29 and 52%, respectively. Achlorhydria was not related to the degree or duration of the alcohol addiction, and did not occur in greater frequency in subjects having macrocytic anemia or showing the greater degree of liver dysfunction. We have discussed the possibility of an achlorhydria preventive factor being a part of the vitamin B complex but not identical with either the vitamin B or the pellagra preventive fraction. We conclude that:

1. Alcohol *per se* does not cause achlorhydria in the alcohol addict.
2. An achlorhydria preventive factor is probably present in the vitamin B complex.

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ROENTGENOGRAPHIC STUDIES OF THE MUCOUS MEMBRANE OF THE COLON.

III. Mucosal Detail Studies as an Aid in the Early Recognition of Carcinoma of the Colon.

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The detection of growths in the colon has always been attended by great difficulty and in many instances with great uncertainty. We are all familiar with cases where repeated routine Roentgen ray examinations both by the oral method and by means of the barium enema have failed to furnish adequate information, thereby causing us to overlook the presence of a carcinoma. Such experiences are embarrassing to the physician and unfortunate for the patient. This situation has been so keenly felt both by surgeons and clinicians that it is quite needless to cite supporting statistics.

We have attempted to perfect a method which will lessen this possibility of error. There are two main factors responsible for the difficulties encountered in the Roentgen ray diagnosis of the large intestines. The first is anatomic, due to such causes as spasm, congenital and acquired adhesions, malpositions and redundancy. Over such causes, the roentgenologist has but limited control. The second factor is that of the method itself which is employed to detect such lesions, roentgenographically. It is this factor which can be so improved as to give the necessary aid in diagnosis.

It is our purpose to describe a method of "mucosal detail" study which has been in use rather extensively abroad but which has not received the attention in this country that it deserves. The greater amount of the work in this field has, of course, been done with

respect to the mucosa of the stomach. In this field the pioneer work of Kalkbrenner,[4] Berg[1a] and Knothe[5] deserves mention.

Various methods have been described from time to time to enable the roentgenologist to visualize more clearly lesions of the colon and sigmoid. The early work of Fischer[2] on the double contrast enema has yielded excellent results in visualizing such lesions as polyps, small adenomas or early fungating neoplasms which might be completely lost to view by the single contrast enema because of the fact that by this latter method the lesion is usually completely surrounded and hidden by the dense opaque column of the barium mixture. Weber[9] more recently has revived this method particularly in demonstrating polypoid lesions and polyposis of the large intestines. Especially in constricting lesions of the colon is this method of double contrast medium of extreme value. Gershon-Cohen and Shay,[3] using the double contrast enema, found that with respect to neoplasms of the large intestines, there is no advantage in using this method where the lesion is moderately or far advanced. In their experience, it was most valuable in detecting early intraluminal neoplastic processes which single contrast does not reveal.

Various manipulations have been advocated as a means of clearing away redundant coils of gut and thus helping in the detection of filling defects. Stewart and Illick[8] advocated the examination of the colon by the oblique roentgenograms and roentgenoscopy, when only the pelvic colon contains barium. By this means they have been able to overcome defects due to such causes as coils of terminal ileum containing barium, low position of the cecum and redundancy of the sigmoid. By their method the sigmoid, posterior rectum and anal region are clearly outlined.

When it comes to the consideration of very early changes in the mucosa of the large bowel, none of the above methods seem to be adequate enough to demonstrate such changes. Yet it is in these very cases of early neoplastic change and infiltration that the early surgical removal of the lesion holds out the greatest hope for cure. The routine barium clysma employed for the Roentgen ray of the colon causes a moderate distention of the viscus, so that only the edges of the gut are visualized. It is only after a certain amount of emptying of the colon has taken place that the actual details of the mucosal folds are obtained. Such studies have been reported by Berg[1b] and Maingot, Sarasin and Duclos.[7] However, use of this method as a routine procedure, to the exclusion of all other methods, is not the intention or purpose of our present report, for the very reason that it requires much time, patience and perfection of technique in order to obtain satisfactory results. The effort is well rewarded when employed in very early infiltrative lesions of the colonic mucous membrane which are attended by the best and most favorable results by surgical removal. It is, therefore, incumbent

upon both the clinician and surgeon to be sufficiently conversant with the possibilities of this method in such early lesions in order to insist upon its more frequent use.

Recently we[6] reported such mucosal studies as observed in the normal colon. The appearance of the mucosal pattern differs somewhat in the different parts of the colon. Thorough familiarity with this normal appearance is absolutely essential for the detection of abnormalities in this mucosal pattern.

Method of Procedure. The first essential for the proper execution of this method is to have as clean a colon as is possible. To effect this the preparation of the patient begins a day previous to the actual examination, during which time only a light low-residue diet is allowed. In the evening before the examination a dose of milk of magnesia or cascara is given. The following morning two enemas containing about a quart of water with some Castile soap is used at 1-hour intervals. Two to 3 hours after the last enema, the patient is ready for examination. A cup of tea or coffee may be allowed in the morning but nothing else. The barium enema itself consists of about 1 quart of a barium mixture prepared in plain water. No milk or mucilage is to be used in the preparation of this solution as they tend to delay the evacuation of the colon.

The slow administration of the barium enema is then started under proper fluoroscopic control, in order to detect the presence of stenosing lesions immediately. As soon as the tip of the contrast material has reached the hepatic flexure of the colon it is discontinued. The patient is then instructed to turn on his right side. Very often the barium will fill out the cecum without giving more barium. Too much contrast material if administered will not only cause distress but in many cases results in leakage into the small intestine. When this has occurred, the subsequent evacuation of the large bowel upon which the success of this method depends will be seriously hindered and will make proper mucosal study almost impossible. A film is then taken with the patient lying on his abdomen. The patient is then instructed to evacuate as much of the barium enema as possible. Repeated fluoroscopic examination is then made to determine whether the correct amount of barium is present to outline the mucosal wall. Sometimes the period of evacuation may take 30 to 45 minutes. Naturally, no technician can be intrusted with this procedure.

We have selected 3 cases for detailed report and have particularly employed both the routine barium enema and the special technique described above in order to demonstrate effectively how lesions which are ordinarily unobserved with the routine enema and were missed by others on previous examination, were distinctly demonstrable by the method of mucosal detail study.

Case Reports. CASE 1.—A male, aged 55, was first seen in April, 1934, complaining of gaseous distention and a certain amount of gastric distress together with general abdominal discomfort, following meals. He had had these symptoms with increasing severity for the previous 6 months. During this period his appetite had remained fair, although he had lost 5 pounds. He gradually developed signs of general weakness and would tire very easily upon the slightest exertion. Two complete gastro-intestinal Roentgen ray series were done during this time but failed to reveal any lesion. The last one was performed 3 weeks before the patient came under our observation. Examination revealed a moderate secondary anemia.

FIG. 1.—Case 1. The appearance of the colon as outlined by the routine barium enema. No defects are discernible in this plate.

FIG. 2.—Case 1. The appearance of the colon as brought out by the mucosal detail method, showing a defect indicated by arrows, which had been missed by the routine barium enema.

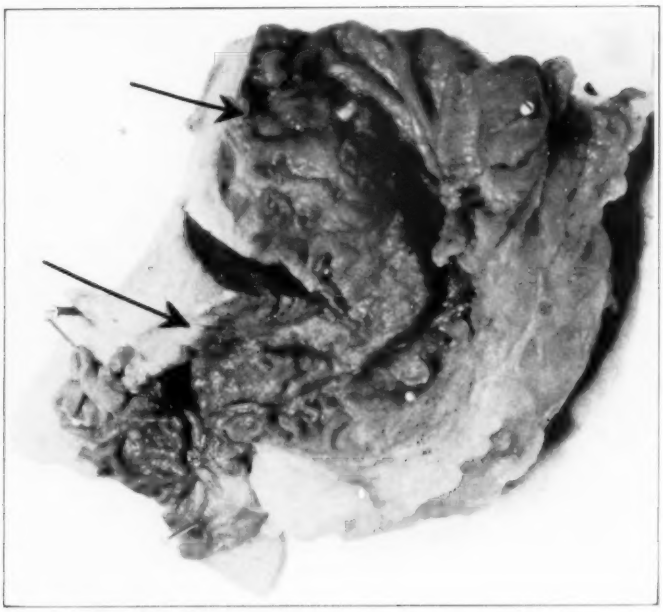

FIG. 3.—Case 1. Specimen of resected colon, showing normal mucous membrane at arrows, with carcinomatous invasion between these points.

FIG. 4.—Case 2. The outline of the carcinoma as obtained by the mucosal detail method. This was completely obscured by the routine barium enema.

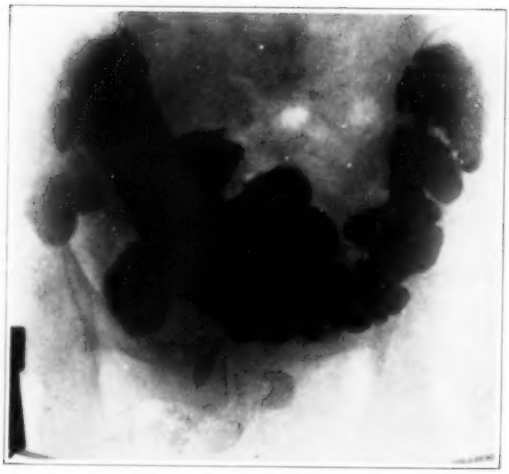

FIG. 5.—Case 3. Appearance of colon after oral administration of barium. No defect discernible.

FIG. 6.—Case 3. Appearance of colon after routine barium enema. Obstruction encountered suggestive of colon telescoped into sigmoid, indicated by arrow.

FIG. 7.—Case 3. Appearance of colon by means of mucosal detail method. Carcinoma clearly outlined, located at the head of the intussusception.

The abdomen was distended but no masses could be felt. There was no glandular enlargement present. Rectal examination was negative. The sedimentation rate was 25 mm. in 1 hour.

Roentgen ray examination revealed the following: The barium enema filled the colon without delay (Fig. 1). This failed to show any filling defect that would indicate malignancy. Study of the mucosa by the method just described (Fig. 2) showed a break in the mucosal fold, about 12 cm. from the anus, extending for a distance of about 3½ cm. Proximally to this defect the mucosa was entirely normal. The patient was operated upon and a cancer of the rectosigmoid junction was found and successfully removed (Fig. 3). The patient made an uneventful recovery and a recent follow-up found him in good condition.

Case 2.—A woman, aged 55, complained of periodic attacks of diarrhea of 6 months' duration. She also had attacks of abdominal pains and gaseous distention. She had lost 5 pounds over 3 months. Careful examination failed to reveal any significant findings, except a positive paratyphoid B culture from the stools. She was treated accordingly for 6 weeks. The abdomen was moderately distended and some tenderness was elicited in the left lower quadrant. No definite tumor mass was palpated. Roentgen ray examination of the colon by means of the routine barium enema showed a complete filling of the colon without any delay. The form and shape of the colon appeared to be normal in this film. No filling defects were noticeable. Examination of the colon, however, by the mucosal method (Fig. 4), revealed a definite defect, 4½ cm. in diameter, in the midsigmoid region. Destruction of the mucosal pattern in this area was easily recognized. Operation confirmed the diagnosis of sigmoid cancer which was successfully removed.

Case 3.—A woman, aged 68, complained of rectal bleeding of 2 weeks' duration. She had a secondary anemia and complained of much weakness and abdominal distress. Roentgen ray examination of the stomach was entirely negative. The barium reached the colon in 24 hours and there was no evidence of any lesion in the colon from this picture (Fig. 5). With the administration of the ordinary barium enema, however, an obstruction was encountered in the middle region of the sigmoid (Fig. 6). The contour of the adjacent sigmoid showed the normal outline. On closer observation, however, one noticed an area of decreased density in the upper portion of the sigmoid which extended for about 6 cm. This finding is very suggestive of invagination of the colon into the sigmoid. The mucosal detail film (Fig. 7) showed a large rounded mass which proved to be a carcinoma which had produced the invagination.

Discussion. Like all laboratory procedures, Roentgen ray examination of the colon is a valuable diagnostic aid, if all possible information can be obtained from it. Too many of us have experienced the embarrassing and unfortunate instance where the existence of a carcinoma of the colon was undetected by the ordinary routine barium clysma. This seems particularly true of small early invading lesions where the surgical results should be at their best. Examination of the films presented in this report shows clearly how it is practically impossible in the majority of cases to make visible such carcinomatous lesions by the ordinary routine barium enema. There are several reasons for this difficulty: (1) With the routine barium enema, there is invariably produced a marked exaggeration in the so-called redundancy of the colon with its consequent over-

lapping of intestinal loops. With the mucosal method this tendency is greatly reduced. (2) With the routine enema, only the edges or borders of the gut are visible and if one is fortunate enough to obtain some irregularity in this outline, the lesion may be detected. With the method which we have described, however, the actual mucosal surface is visible. (3) Various displacements and distortions of the flexures are invariably the result of the complete filling of the colon by the barium or air. (4) The degree of contractility and elasticity of the colon can only be determined by the mucosal method and is completely obscured by the use of the routine barium enema.

In Case 1, for example, the patient had been carefully Roentgen rayed on two previous occasions without any abnormality being detected. Likewise, when the routine barium enema was employed by us, a similar negative result was obtained (Fig. 1). The contrast between this picture and Fig. 2 shows very clearly the comparison of results obtained by the two methods. Had the mucosal method not been done at this time, a third negative report would have been made which would certainly have changed the end result in this case. Likewise Figs. 5, 6 and 7 show the same experience in Case 3.

The repetition of such similar experiences makes us enthusiastic in advocating the use of this method of mucosal study of the colon. We do not wish to convey the impression, however, that it should be used routinely to the exclusion of all other methods. There are cases, for example, as in constricting lesions, where the double contrast medium will give more information than mucosal study alone.

The "mucosal detail" method is described and presented here as offering a means of additional study in a part of the intestinal tract where carcinoma lesions are very often overlooked until they have reached an advanced stage of growth. If used properly in this way, we believe that mucosal detail studies will prove of invaluable help in the early recognition of carcinomatous infiltration of the colon mucosa.

Conclusion. A method is described for obtaining mucosal detail studies of the colon. With the aid of this procedure more information is obtained than when the routine barium enema is employed, and as a result of this, cases of carcinoma of the colon which may be ordinarily missed by the routine barium enema are detected. This method enables detection of the carcinoma at an early stage, when the tumor is still small. The importance of such detection becomes most significant when it is realized that early recognition of the carcinoma offers the only possible hope for cure. Many of the failures of early detection are due to the inadequacy of the usual barium enema. Three cases are described in detail showing the comparative values of the two methods.

This method is not advocated as a routine procedure, but as a diagnostic aid in doubtful cases. The technique requires considerable experience and cannot be intrusted to a technician.

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TUBERCULOUS TRACHEOBRONCHITIS: ITS PATHOGENESIS.

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Pulmonary tuberculosis so overshadows its secondary manifestations that, with the exception of laryngeal involvement, lesions of the mucosa of the respiratory tract have tended to pass unnoticed and unappreciated. During the past 3 years the attention of the staff of the Tuberculosis Unit of the University Hospital has been drawn to a group of patients who have developed dyspnea, a wheezing respiration, cyanosis and intractable coughing in the course of pulmonary tuberculosis. In some instances these signs have appeared when the pulmonary lesion apparently had been retrogressing satisfactorily. Impressively, these patients have done poorly with any type of collapse therapy. In spite of every effort, mortality in this group has been high, 47% of the group showing tracheobronchial ulcers or stenoses being dead within a year after the diagnosis had been established.

The clinical manifestations of this complication and the bronchoscopic appearances of the tracheal and bronchial mucosæ are being presented elsewhere by Littig, Barnwell, Culp and Samson.[1, 10] Since the appreciation of the occurrence of these lesions, the diagnosis has been made in 33 cases; of these, bronchoscopy has been

done in 24 cases, while in the rest the clinical signs have been so prominent as to make the diagnosis a practical certainty. In this entire group only 1 patient can be said to have shown any improvement; the others are either already dead or are progressing steadily downward.

Historical. One finds little mention of this complication in recent pathologic literature and the clinical discussions of the complications of pulmonary tuberculosis are usually entirely silent with respect to it. Nevertheless, Eppinger[3] was familiar with this type of tuberculosis and in the volume devoted to the larynx and trachea, published in 1880 as volume II of Kleb's *Handbuch der pathologischen Anatomie*, he gave an excellent description of the tracheal lesions occurring occasionally in those dying of pulmonary tuberculosis. In his experience, about one-eighth of the cases without laryngeal lesions showed ulcerative tuberculous tracheitis. He was impressed by the relatively greater frequency of involvement of the lower portion of the trachea. This he attributed to extension from the main bronchi which in turn he considered to have been involved by direct extension from the surrounding lung and caseating bronchial lymph glands. That fibrosing and stenosing tracheal tuberculosis had not been encountered was due, he thought, to the brevity of life consequent upon the establishment of this complication. He remarked upon the tendency for the lesions to be most abundant along the posterior wall.

Although not as cogently discussed as by Eppinger, this condition was mentioned during the previous year (1879) by Heinze.[7] Nothing of consequence appears to have been added to the subject until 1904 when Hedinger[6] presented a case which he considered to be primary tuberculosis of the trachea and bronchi. This was in a man, aged 29, with a 3-year history of chronic tracheitis and laryngitis with progressive laryngeal stenosis necessitating tracheotomy, following which he died. Autopsy showed the tracheal wall to be tremendously thickened, with marked reduction of the lumen. The process continued into the bronchi and throughout was characterized by large ulcers. The pulmonary involvement was slight and considered by Hedinger to be bronchogenous.

In the discussion of Hedinger's paper, Hansemann[4] cited an instance of primary tracheal tuberculosis in a man, aged 75, not a single tubercle being found elsewhere than in the trachea.

On the same occasion, Schmorl[11] told of 2 cases which he considered primary tracheal tuberculosis, 1 being a youth, aged 18, the other a child of 8 years.

At this time interest in the subject was largely centered in the problem of primary tracheal tuberculosis, an additional case being presented in 1913 by Donagány.[2] The progressive ulcerative tracheitis described long before was considered of interest only in the autopsy room. The clinical implications of the condition were generally ignored so that when tracheal and bronchial tuberculosis was mentioned at all, the allusion was casual and perfunctory. Kaufmann[8] and also Hart and Meyer[5] devoted scant attention to the subject, their treatment being somewhat less complete than that of Eppinger over half a century before.

Recently (1934) Reichle and Frost,[9] treating of tuberculosis of the major bronchi, have distinguished various mechanisms in the establishment of ulcerative tuberculous bronchitis. Frequently they observed tubercles in conjunction with the submucosal mucous glands and concluded that the infection was carried from the neighboring lung to the bronchial mucosa by way of these glands. For reasons not at all clear, they called this mechanism "infection by contiguity." A second mode of involvement they designated as "infection by implantation," in this instance using the

phrase in its usual definition. They considered this form to be practically limited to the lower lobe bronchi. In the upper lobes they designated the mucosal and submucosal involvement as "infection by continuity."

Pathologic Study. In order to obtain data on the frequency of tuberculous tracheobronchitis and to demonstrate, if possible, its pathogenesis, a study was made of the clinical records, protocols and microscopic slides of 122 cases of pulmonary tuberculosis coming to autopsy. The only selective criteria employed in isolating this group were: (1) That the primary cause of death should have been the tuberculosis and (2) that permission for complete autopsy had been obtained. Thus a series was obtained complete with respect to tissues from the larynx, trachea, bronchi and bronchial lymph glands, in addition to representative blocks from all involved regions of the lungs.

One or 2 sections from the larynx, 1 to 3 from the trachea and 1 each from the large bronchi and bronchial lymph glands were prepared, the blocks being selected to show any gross lesion. If no such lesion were apparent, then the blocks were chosen at random from the regions cited.

Statistical Study. Since such material at once raises a question concerning the adequacy of the sampling, especially in the trachea where the area is large, the entire respiratory tracts from 8 fatal cases of pulmonary tuberculosis were isolated and 12 transverse serial blocks made from each trachea. The blocks were numbered consecutively from above downward. One section was prepared from each block and examined for evidence of tuberculosis, routine hematoxylin and eosin stains being employed. A trachea was recorded as tuberculous in which any section exhibited histologic signs of the disease.

The results of this study (Table 1) disclosed a marked tendency for tuberculous involvement, when it occurs, to be spread over the

TABLE 1.—PULMONARY TUBERCULOSIS. TUBERCLES IN SERIAL BLOCKS OF TRACHEA (TEST SERIES).

Serial levels.	Autopsy No. A-223-AG.	A-309-AG.	A-36-AJ.	A-351-AH.	A-226-AI.	A-289-AI.	A-78-AK.
1	−	−	−	+	−	−	+
2	−	−	−	+	−	+	+
3	−	−	−	+	−	+	+
4	−	−	−	+	−	+	+
5	−	−	−	+	−	+	+
6	−	−	−	+	−	+	+
7	−	−	+	+	−	−	+
8	−	−	+	+	−	−	+
9	−	−	−	+	−	−	+
10	−	−	+	+	−	+	+
11	−	−	+	+	−	+	+
12	−	−	−	+	−	−	+

entire tracheal mucosa. This was further emphasized by the distribution of the tubercles which tended to be moderately uniform with respect to successive levels. Furthermore, in this test series, as well as in the larger series generally, the tuberculous involvement appeared to be chiefly in the posterior wall. Well over two-thirds of the tubercles were to be found in the posterior one-half of the trachea.

It is evident that in 5 of the tracheas of this series the random selection of any one of the 12 sections would completely represent the entire trachea with respect to the presence or absence of tuberculosis, assuming, for simplification, that the 12 sections themselves completely represented the trachea. In 2 cases some of the sections exhibited tubercles, while others of the series did not.

If agreement between the individual section and the character of the series from one trachea be considered a success, and a disagreement a failure in the probability sense, then of the 84 sections there are 71 successes and 13 failures. The probability that a section chosen at random will accurately describe the entire trachea with respect to the presence or absence of tubercles is $\frac{71}{84}$ or 0.845 ± 0.026 where 0.026 is the probable error of the prediction $\left(0.6745\sqrt{\frac{pq}{n}}\right)$. Since in the larynx and bronchi one section represents a much greater proportion of the total tissue, the probability of accurate representation by a single section taken at random must necessarily be considerably higher.

The high prediction value of a single section is but another way of expressing a fact consistently appearing throughout this study: that when the tracheal mucosa, in fatal cases of pulmonary tuberculosis, succumbs to the tubercle bacillus, the yielding of the defenses tends to be general so that the entire mucosa, or a large portion of it, becomes involved practically simultaneously.

TABLE 2.—PULMONARY TUBERCULOSIS. MUCOSAL LESIONS. 122 AUTOPSIES.

Region.	Incidence of tuberculosis.	
	No.	Per cent.
Larynx	37	30.4
Trachea	25	20.5
Bronchi	41	33.6
Tract generally (larynx and/or trachea and/or bronchi)	59	48.4
No involvement of tract	63	51.6

In Table 2 is given the incidence of lesions in the various regions, involvement of some portion of the larynx, trachea or large bronchi occurring in 48.4% of the cases. The observed lesions were grossly ulcerative much more frequently in the larynx than in the trachea and bronchi.

The complete distribution of the cases with respect to the various combinations of involvement is given in Table 3. In Tables 4 and 5, the same form is utilized for the segregation of the cases showing or failing to show miliary dissemination. The further statement of the statistical character of the various groups appears in Table 6 where the mean and standard deviation are given for each combination.

TABLE 3.—PULMONARY TUBERCULOSIS. MUCOSAL LESIONS. 122 AUTOPSIES.

Larynx.	Trachea.	Bronchi.	No. of cases. Male.	Female.	Total.	
−	−	−	38	25	63	
−	−	+	11	3	14	
−	+	−	3	1	4	
−	+	+	0	4	4	
						− 85
+	−	−	7	2	9	
+	−	+	5	6	11	
+	+	−	4	1	5	
+	+	+	6	6	12	
			—	—		− 37
			74	48		122

TABLE 4.—PULMONARY TUBERCULOSIS. MUCOSAL LESIONS. AUTOPSIES. 27 MILIARY CASES.

Larynx.	Trachea.	Bronchi.	No. of cases. Male.	Female.	Total.	
−	−	−	11	10	21	
−	−	+	2	0	2	
−	+	−	1	1	2	
−	+	+	0	0	0	
						− 25
+	−	−	0	1	1	
+	−	+	0	0	0	
+	+	−	1	0	1	
+	+	+	0	0	0	
			—	—		− 2
			15	12		27

TABLE 5.—PULMONARY TUBERCULOSIS. MUCOSAL LESIONS. AUTOPSIES. 95 NON-MILIARY CASES.

Larynx.	Trachea.	Bronchi.	No. of cases. Male.	Female.	Total.	
−	−	−	27	15	42	
−	−	+	9	3	12	
−	+	−	2	0	2	
−	+	+	0	4	4	
						− 60
+	−	−	7	1	8	
+	−	+	5	6	11	
+	+	−	3	1	4	
+	+	+	6	6	12	
			—	—		− 35
			59	36		95

TABLE 6.—PULMONARY TUBERCULOSIS. 122 AUTOPSIES.

Males.					Females					Totals.				
No. of cases.	Age at death, yrs.		Duration, mos.		No. of cases.	Age at death, yrs		Duration, mos.		No. of cases.	Age at death, yrs.		Duration, mos.	
	Mean.	S.D.	Mean.	S.D.		Mean.	S.D.	Mean.	S.D.		Mean.	S.D.	Mean.	S.D.
Non-miliary Cases.														
59	33.7	14.2	26.1	29.1	36	24.6	13.4	25.4	22.7	95	30.2	14.6	25.8	26.8
Miliary Cases.														
15	30.9	20.7	10.2	8.8	12	16.4	14.2	6.0	4.7	27	24.5	19.4	8.3	7.6
All Cases.														
74	33.1	15.8	22.8	26.9	48	22.5	14.0	20.5	21.5	122	29.0	16.0	21.9	24.9

Superficially, it would appear that the mean ages at death for the females is appreciably different in the miliary and non-miliary groups while the corresponding figures for the males show no such differences. However, if this is considered as a problem in random sampling with selection of groups of 36 and 12 from such a population of 48, it develops that the distribution of the means of such samples would have the following statistical character:

Arithmetic mean	22.52 years
Standard deviation	3.54 "
Skewness	0.0

From this it follows that the actual mean of 24.56 years for the age at death in the non-miliary cases differs from the mean of all random samples by 0.577 standard unit;* that is, the difference in age at death between the miliary and non-miliary groups of females could occur by chance about once in two times. Clearly this difference is insignificant.

When the same analysis is applied to the corresponding male group the same result is obtained, t being 0.602.

With respect to sex there is a very significant difference between the mean age at death for the males compared with the females. Not only does our autopsy series show a marked preponderance of males over females in numbers, but the average age at death for the males greatly exceeds that for the females. While these differences are statistically significant and cannot be ascribed to chance, we have no reason to consider them other than the result of preselection in the patients referred to the tuberculosis unit of our hospital.

When duration of the disease is considered there is again a very significant difference for both sexes. Those cases terminating in miliary dissemination consistently show short durations of the disease, duration here being the time elapsing from the first recognizable sign or symptom of pulmonary tuberculosis until death.

* The standard variate t is: $t = \frac{v - M_v}{\sigma_v}$

Associated, in our opinion, with the short duration in those cases terminating in a miliary dissemination is the relative infrequency of tracheobronchial mucosal involvement in this group, only 5 out of 27 cases showing any lesions whatever. To compare with this, we find that in 95 non-miliary cases, 45 had involvement of the mucosa of the trachea or bronchi.

These 2 groups of cases differ by another factor in addition to duration of the disease. The miliary group is composed of those with proved hematogenous dissemination. The infrequency of involvement of the tracheobronchial mucosa in the miliary group further indicates that the hematogenous route is of no consequence in the establishment of these lesions.

Further examination of these data emphasizes the marked tendency for lesions of the larynx, trachea and bronchi to occur concomitantly. The concurrence of tracheal lesions with laryngeal tuberculosis has led some to the mistaken conclusion that the tracheal involvement is secondary to that of the larynx. If this were true, absence of laryngeal lesions would imply absence of tracheal lesions, a conclusion contrary to fact. In this series there were 8 instances of tracheal tuberculosis in which the larynx was entirely free of such lesions.

The fallacy of considering tracheobronchial mucosal lesions secondary to laryngeal tuberculosis arises from the failure to realize that strong positive correlations do not necessarily imply causal relationship. Events may occur together, not because they are causally related, but because they are all associated with a common factor. In this specific problem the common factor is pulmonary tuberculosis.

Histologic Observations. Inspection of the tracheal and bronchial sections showed that if only 1 or 2 tubercles occurred, these usually were to be found in the posterior portion, and where there were many lesions they were most numerous in this region. Furthermore, the great majority of these lesions were to be found very intimately associated with the mucous glands, either in conjunction with the ducts or in relationship to the secreting alveoli. The lesions were thus relatively superficial.

The usual form of the lesion was that of the small epithelioid tubercle with caseating center. The cellular infiltrate consisted of both polymorphonuclear and mononuclear cells, the former being especially abundant when the tubercle lay close beneath or actually involved the mucosal epithelium. Very small ulcers were found to be associated with immediately subjacent epithelioid tubercles. In larger ulcers showing more tissue destruction no such relationship could be demonstrated. About such lesions, once established, a marked tendency to lateral extension beneath the epithelium was observed, so that ulcerated regions were frequently underlain by more widely extensive tuberculous involvement than the actual

area of ulceration would suggest. Both the tuberculous and non-tuberculous mucous glands showed dilatation of the ducts with markedly increased mucin formation, many neutrophils being free in the secretion.

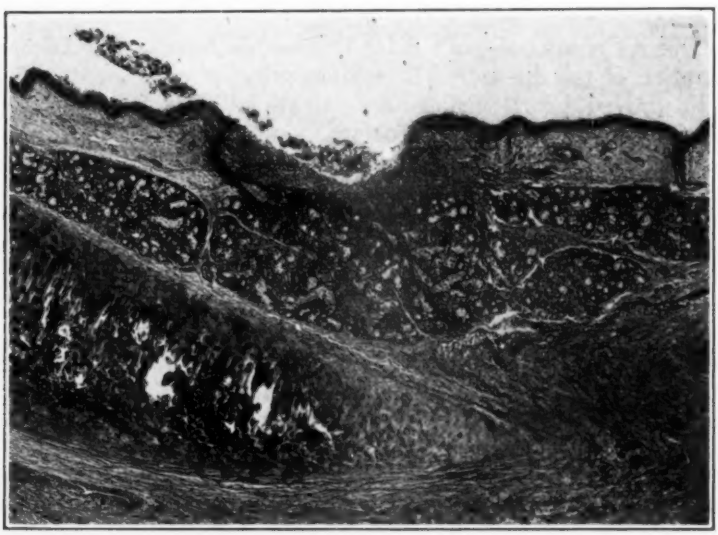

FIG. 1.—Ulcerative tuberculous tracheitis. Small mucosal lesion associated with involvement of mucous glands of posterior portion of trachea. (× 20.)

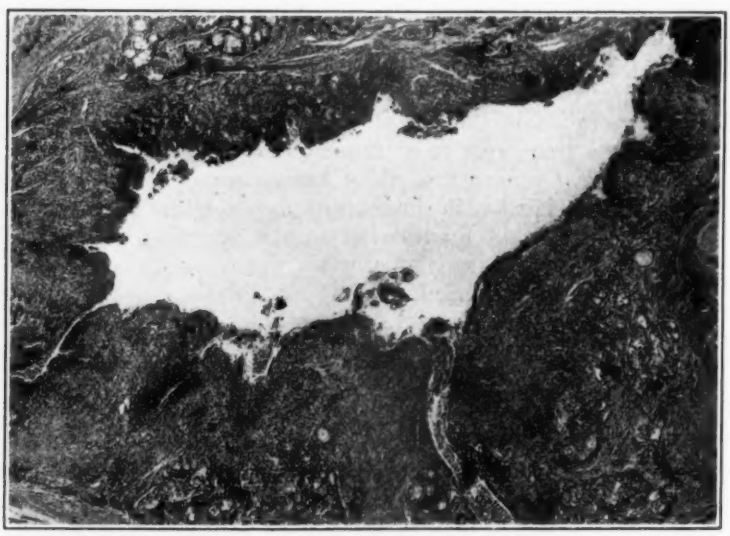

FIG. 2.—Ulcerative tuberculous bronchitis. Marked thickening of mucosa. Early stenosis. (× 10.)

In addition to the granulomatous lesions, in all instances a diffuse chronic inflammation, with edema and fibrosis, was to be found. This process, etiologically not definitive, resulted in thickening of the submucosa to a marked degree, especially in the bronchi where the lumen was frequently sensibly reduced.

The portal of entry of the process in the bronchi is difficult to determine with accuracy. In many instances continuity of tuberculous involvement from nearby lymph nodes to the peribronchial tissues should be readily demonstrated, making entirely reasonable the view that such infections arise by transport of the organisms through the lymphatics from the peribronchial tissue to the submucosa, or by way of the deeply lying mucous glands to the mucosa.

In the trachea, however, this confusion of possible routes was not found to exist. In no instance of tracheal tuberculosis was there diffuse peritracheal tuberculosis and, in many cases, tracheal mucosal lesions occurred without tubercles being found in the nearby peritracheal lymph glands. One is forced to the conclusion that extension from the peritracheal tissues, by any route whatever, is an unimportant mechanism. When it is considered that most of the bronchial lesions were of the same type as seen in the trachea, one is less convinced of the soundness of the argument that such lesions arise predominantly by invasion of the peribronchial tissues.

The incidence of open ulcers depends upon the definition of such a lesion, particularly with respect to size. In 2 instances the entire tracheobronchial mucous membrane had been destroyed, with a continuous tuberculous granulation tissue surface replacing the mucosa throughout the tract. In other instances the areas of ulceration were microscopic and unappreciable to the naked eye. Between these extremes, all gradations in size could be found. The incidence of ulceration, reported for any such series, is thus likely to be dependent upon the circumstances of observation.

Summary. From the data presented it is evident that the occurrence of tracheal tuberculosis is unrelated to hematogenous dissemination. It is further not associated with peritracheal extensions, since many instances of mucosal tuberculosis were found in which both the peritracheal connective tissue and the adjacent lymph glands were entirely free of evidences of the disease.

On the contrary, there was observed a marked tendency for the simultaneous occurrence of tubercles in all portions of the trachea. Further, such lesions exhibited a definite tendency to more frequent occurrence posteriorly in patients who had been recumbent for prolonged periods. These lesions, in their earliest stages, were intimately in association with the mucosal epithelium or the ducts of the mucous glands. With the further observation that all the cases exhibited a sputum rich in tubercle bacilli, we are led to the conviction that the tracheal involvement is predominantly, if not entirely, a matter of implantation or contact infection.

Since, in many of the main bronchi, lesions of the same character were found as in the trachea, it is a reasonable presumption that the same mechanism tends to prevail in these regions. In view of the instances of proved continuity of involvement from the peribronchial tissue, however, it cannot be denied that bronchial mucosal tuberculosis may arise by direct extension from lesions in neighboring peribronchial structures. The latter mechanism appears to be much more important in the intrapulmonary bronchial branches than in the main bronchi.

While tuberculous tracheobronchitis is not causally related to laryngeal tuberculosis, they tend to be concurrent, so that in this series 76% of the cases with tuberculous laryngitis had also involvement of the trachea or bronchi. Where the larynx was free from the disease, 25% of the cases had lesions in the lower portion of the tract. Considering the trachea alone, the above figures become 46% and 9.4%, respectively.

In this autopsy series, while evidences of fibrosis and thickening of the tracheal and bronchial submucosæ were marked, no conclusive evidence of a healed ulcer was discovered, although some of the localized changes were compatible with this interpretation.

In the entire series no instance of presumptive primary tracheal tuberculosis occurred. We are inclined to doubt the existence of such an entity.

Conclusions. 1. In a series of 122 cases of pulmonary tuberculosis studied at autopsy, 50 cases (41%) showed lesions in the trachea, main bronchi or both.

2. The mode of infection of the tracheal mucosa is outstandingly one of contact with bacillary sputum.

3. The immediate portal of entry in the trachea may be either through the epithelium or by way of the ducts of the mucous glands.

4. Infection of the mucosa of the main bronchi is predominantly one of contact, but in an appreciable number of instances the invasion is by direct extension from the peribronchial structures.

5. The complication occurs more frequently in cases in which the pulmonary disease is of long duration.

6. Laryngeal tuberculosis is frequently concurrent with tracheobronchial mucosal spread but not causally related to it.

7. Involvement of the tracheobronchial mucosa, when it occurs at all, tends to be widespread and most marked along the posterior wall.

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OBSERVATIONS ON THE USE OF CARBON DIOXIDE IN EARLY PNEUMONIA.

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Inhalation of carbon dioxide, diluted either with oxygen or merely with air, is now a well-established therapeutic and prophylactic measure in surgery to prevent or counteract pulmonary complications,[4c] and in obstetrics to overcome neonatal atelectasis.[4d] Its chief value lies in inducing such an inflation of the lungs that the airways are cleared, natural drainage established and the lungs freed of infective matter.[5] In internal medicine and pediatrics, on the contrary, inhalation of carbon dioxide has not yet received a sufficient trial to determine to what extent it may be of value also in these fields, particularly at the onset of pulmonary infection.

In justification of a trial of this inhalation in early pneumonia, it may be recalled that this therapy has largely eliminated the postoperative pulmonary complications that were formerly grouped indiscriminately under the term "postoperative pneumonia," regardless of whether they were merely atelectatic or truly pneumonic. It has not only made the problem of initiating respiration in the asphyxial newborn far simpler for the obstetrician than it formerly was, it has given him the most effective means now known of combating the tendency to subnormal respiration, cyanosis and the development of pneumonia, particularly in weak or premature babies that formerly induced a considerable mortality.[2]

Internists have been disinclined to the idea that inhalation of carbon dioxide might be of value in the treatment of pneumonia, on the ground that mere deep breathing would obviously be incapable of removing the consolidated exudate of the pneumonic lung as seen at autopsy.* But if inhalation of carbon dioxide has any value, it lies primarily in the prevention of that accumulation of exudate before its consolidation, that is, before the ill effects of occlusion have had time to reach full development. If bronchial occlusion is the critical factor in the accumulation of exudate that

* Coryllos, in a recent personal communication, has observed that carbon dioxide liquefies pneumonic exudate with great rapidity *in vitro*.

an increasing number of observers claim, it is of prime importance that the airways should be kept open. And only three means are now known to open and clear the airways, and thus establish drainage: 1, by use of the bronchoscope; 2, by frequent changes of the patient's position, and, 3, by inhalation of carbon dioxide.

Whatever the method employed there are already grounds worthy of serious consideration indicating that clearing of the airways in the early stages of pneumonia may abbreviate or even abort the disease. Henderson,[4b] who has been chiefly responsible for the introduction of the inhalational method of resuscitation from asphyxia and for the relief of postoperative pulmonary complications, has truly said that at least in all secondary pneumonias "internists would do well to borrow from surgery one of its major axioms: a well-drained infection is relatively harmless; an occluded infection is always dangerous." Coryllos[1] has demonstrated experimentally that bronchial occlusion may be a factor of critical importance in the development of an acute pulmonary infection. And Chevalier Jackson[6] has demonstrated clinically that the use of the bronchoscope early in pneumonia may produce a rapid recovery.

Not every hospital has in its service a skilled bronchoscopist. But in every hospital now there is an anesthetist who is conversant with the administration of carbon dioxide; and it is a technique that the internist easily acquires.

Comparison of Treatments. These considerations seemed to the writers to afford an adequate basis for the trial clinically of the administration of carbon dioxide to such cases of pneumonia as came to the hospital in the early stages of the disease. And we report herewith the results of our observations.

As a background we present in Section A of Table 1 the mortality during 5 years of the pneumonia patients who came under our observation and who received no inhalational treatment. In Section B of that table is shown the mortality of patients who early in the disease received inhalation of oxygen, or of carbogen (5% carbon dioxide in oxygen) by means of a tent. Little or no hyperpnea was thus induced. This group also includes those patients who received carbon dioxide inhalational therapy more than 72 hours after the onset of illness. In Section C are given the comparable figures for patients who were early treated with brief but repeated inhalations of carbon dioxide in sufficient concentration to induce marked temporary hyperpnea. The mortalities in the 3 groups were: (*a*) For those without inhalation, 17%; (*b*) for those with early inhalation of oxygen or carbogen or inhalation of carbon dioxide late in the illness, 16%; and (*c*) for those with early inhalation of carbon dioxide, 4%.*

* This series originally included 121 patients in the untreated (A) and 48 patients in the treated group (C). Of these 9 were excluded in the first and 1 in the last group. These patients were primarily treated for heart failure, but died with a terminal pneumonia. If these patients were included in the statistics the mortalities would read 23.1% in Group A and 6.4% in Group C, respectively.

TABLE 1.—CASES OF BRONCHOPNEUMONIA AND LOBAR PNEUMONIA AND THOSE WHO DIED (A) WITH NO CO_2 INHALATIONAL TREATMENT; (B) WITH INHALATION OF OXYGEN OR CARBOGEN (5% CARBON DIOXIDE IN OXYGEN) OR CO_2 LATER THAN 48 HOURS AFTER ONSET, OR WHEN ADMINISTERED IN QUANTITIES INSUFFICIENT TO CAUSE VENTILATION; AND (C) WHEN CARBON DIOXIDE WAS ADMINISTERED EARLY BY THE METHOD HERE DESCRIBED.

W = Months of November to April, inclusive.
S = Months of May to October, inclusive.

Treatment.		1931.		1932.		1933.		1934.		1935.*		Total.	Mortality, %
		W	S	W	S	W	S	W	S	W	S		
(A)	Broncho-	3	4	19	7	10	7	9	2	7	7	75	
	Lobar	5	0	8	3	3	0	7	3	5	3	37	
	Total	8	4	27	10	13	7	16	5	12	10	112	
	Deaths:												
	Broncho-	1	0	3	1	0	2	1	0	1	1	10	
	Lobar	0	1	1	0	1	0	2	1	2	1	9	
	Total	1	1	4	1	1	2	3	1	3	2	19	17.0
(B)	Broncho-	1	1	8	7	4	2	1	1	2	2	29	
	Lobar	0	0	2	1	2	1	1	0	1	0	8	
	Total	1	1	10	8	6	3	2	1	3	2	37	
	Deaths:												
	Broncho-	0	1	1	0	1	1	0	0	1	0	5	
	Lobar	0	0	0	0	0	1	0	0	0	0	1	
	Total	0	1	1	0	1	2	0	0	1	0	6	16.2
(C)	Broncho-	2	0	6	4	3	6	6	1	3	2	33	
	Lobar	0	1	3	1	3	1	2	0	2	0	13	
	Total	2	1	9	5	6	7	8	1	5	2	46	
	Deaths:												
	Broncho-	0	0	0	0	0	0	0	0	0	1	1	
	Lobar	0	0	0	0	0	0	1	0	0	0	1	
	Total	0	0	0	0	0	0	1	0	0	1	2	4.3

* Figures for 1935 are for the first 8 months only.

Equally favorable to this treatment are the figures for the days that hyperpyrexia continued in these three classes of cases, as shown in Table 2 for Group A (no inhalational CO_2 therapy), Table 3 for Group B (inadequate inhalational CO_2 therapy), and Table 4 for Group C (adequate inhalational CO_2 therapy). In the cases of bronchopneumonia the three classes had an average duration of fever of (*a*) 11.5 days, (*b*) 10.3 days and (*c*) 4.3 days, respectively. In the cases of lobar pneumonia the figures were (*a*) 13.7 days, (*b*) 11.7 days and (*c*) 5.2 days of fever, respectively.

Technique of Inhalation. The patients who received no inhalation were for the most part those who were not seen early enough for us to hope that this treatment would be effective. Others who were seen early enough, however, were given the conservative oxygen inhalational and symptomatic treatment. Otherwise they were entirely comparable to cases to which inhalation was administered.

The cases treated with early inhalation of oxygen showed, as might be expected at that stage of the disease, no perceptible effect (Table 2). Those treated early with carbogen also were only slightly affected, and as this inhalation is relatively expensive it was abandoned (Table 3). Our observations should not, however, be interpreted as weighing against the administration of either oxygen or carbogen for the relief of anoxia in later stages of pneumonia.

The advantages in using carbon dioxide alone are many: It is inexpensive; it comes in small tanks that are easily transported; and it can be administered to the patient without the discomfort

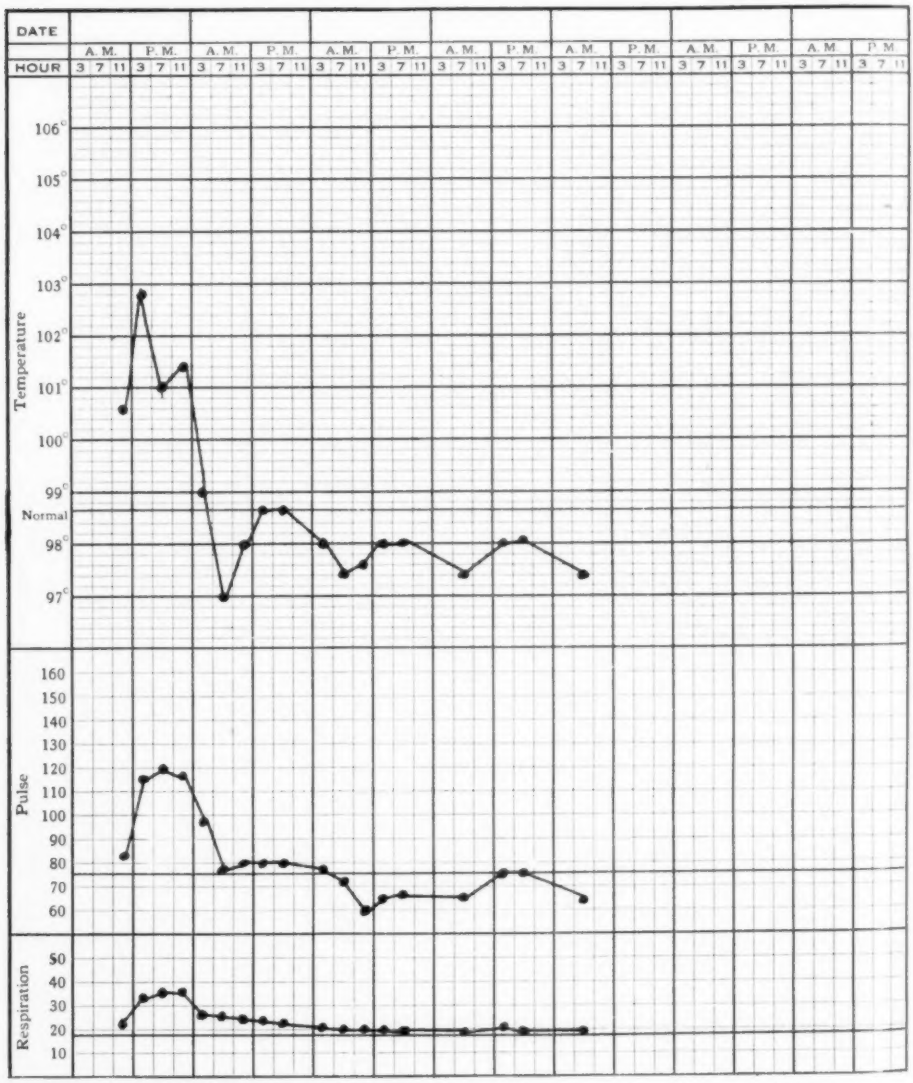

FIG. 1.—Case 16788. Male, aged 20; bronchopneumonia. Upper respiratory infection for 10 days. Cough, weakness, fever and blueness of lips was then noted. On examination: Temperature, 102.8° F.; pulse, 20; respiration, 32. Cyanotic and dyspneic; dullness at left base with patchy areas of diminished breath sounds and voice sounds. Fine râles at both bases. Patient looked very ill, and prognosis was charted as guarded. Urine, negative. W.B.C., 18,700. Polys, 77.5. Treatment: CO_2 inhalations every hour while awake, and every 2 hours during the night. Crisis: Within 24 hours. Notes: Symptomatic improvement took place next day. Lungs cleared up 6 days after admission.

TABLE 2.—DAYS OF DURATION OF FEVER IN 112 PATIENTS WHO RECEIVED NO CO_2 INHALATIONAL TREATMENT, OF WHOM 93 RECOVERED AND 19 DIED.

Days of fever.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.
Broncho-	0	1	3	5	6	4	7	6	0	8
deaths	0	1	1	0	2	2	0	0	0	0
Lobar	0	0	0	1	1	4	8	3	3	1
deaths	0	0	0	0	1	2	3	1	1	1
Total cases	0	1	3	6	7	8	15	9	3	9
Total deaths	0	1	1	0	3	4	3	1	1	1

Days of fever.	11.	12.	13.	14.	15.	16.	17.	18.	19.	20.
Broncho-	5	2	6	6	1	1	2	1	1	1
deaths	0	0	0	1	0	0	0	0	0	0
Lobar	3	1	3	1	0	0	0	0	1	1
deaths	0	0	0	0	0	0	0	0	0	0
Total cases	8	3	9	7	1	1	2	1	2	2
Total deaths	0	0	0	1	0	0	0	0	0	0

Days of fever.	21.	22.	23.	24.	25.	26.	28.	30.	49.	90.
Broncho-	1	3	1	1	0	1	0	0	1	0
deaths	0	2	0	0	0	0	0	0	0	0
Lobar	1	0	0	1	2	0	1	1	0	1
deaths	0	0	0	0	1	0	0	0	0	0
Total cases	2	3	1	2	2	1	1	1	1	1
Total deaths	0	2	0	0	1	0	0	0	0	0

Average days of fever: Bronchopneumonia, 11.5; lobar pneumonia, 13.7.

and sometimes the anxiety that the use of a tent involves. In all of our cases this gas was administered by the "drip" method introduced by Dr. Arthur Guedel for the prevention of postoperative pulmonary complications in this hospital.* The technique is as follows:

A linen towel is folded in half, along its length. It is then wrapped around the patient's head and face from the chin to the

TABLE 3.—DURATION OF FEVER (DAYS) IN 37 PATIENTS TREATED WITH OXYGEN OR CARBOGEN (5% CARBON DIOXIDE IN OXYGEN) OR CO_2 ADMINISTERED IN MOST INSTANCES LATER THAN 48 HOURS AFTER ONSET, OR EARLIER IN QUANTITIES INSUFFICIENT TO CAUSE VENTILATION, OF WHOM 31 RECOVERED AND 6 DIED.

Days of fever.	5.	6.	7.	8.	9.	10.	11.	12.	14.	15.	16.	17.	19.	20.	28.	30.
Broncho-	1	1	2	3	1	3	2	2	3	3	2	1	2	1	2	1
Deaths	1	0	1	2	0	0	0	0	1	0	0	0	0	0	0	0
Lobar	0	1	0	0	2	0	0	1	1	1	0	1	0	0	0	0
Deaths	0	1	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Total cases	1	2	2	3	3	3	2	3	4	4	2	2	2	1	2	1
Total deaths	1	1	1	2	0	0	0	0	1	0	0	0	0	0	0	0

Average days of fever: Bronchopneumonia, 10.3; lobar pneumonia, 11.7.

vertex, so that a shallow cup is formed with the face as the base and the towel forming the sides. The gas is run at the rate of about 3 liters per minute. In the absence of a flow meter, a steady, soft stream which hits the hand without force generally suffices. The patient is instructed to open the mouth and breathe deeply.

* Quantitative apparatus and an open mask from designs of Dr. Yandell Henderson are made by the Foregger Company, New York, and the Ohio Chemical and Supply Company, Cleveland.

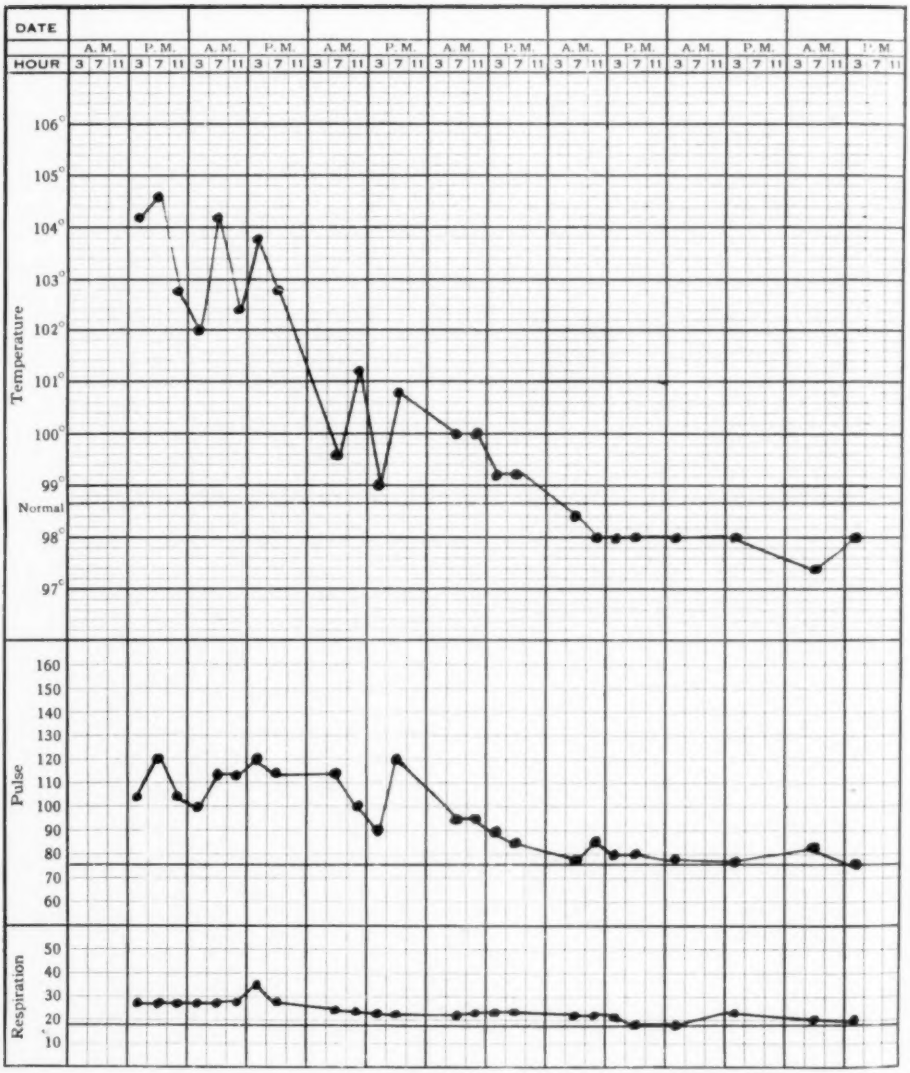

FIG. 2.—Case 4989. Male, aged 14; lobar pneumonia. Sudden onset with a chill. On examination: Temperature, 103° F.; pulse, 104; respiration, 28. There was lagging and dullness of the left chest; breath sounds were slightly suppressed at both bases, and crepitant râles were audible at the left base. Treatment: He was admitted to the hospital within 36 hours after onset of chill and placed in a carbogen tent where he breathed an atmosphere of 5% CO_2 and 95% O_2. The following morning there were dullness and râles present at both bases and breath sounds were tubular at the left base. Roentgen ray report: Lobar pneumonia. After 12 hours of carbogen therapy the tent was removed and he was given inhalations of CO_2 gas every 2 hours. Notes: Temperature became normal on the fifth day. Physical signs remained for 10 days after admission to the hospital.

The end of the flexible rubber tube is held about 2 inches over the tip of the nose. The gas is then allowed to run until the patient develops a hyperpnea which the observer can see is wholly out of voluntary control. The hyperpnea is continued under the gas for about 1 minute when the administration is discontinued, but the towel around the face is not removed. The hyperpnea continues for 1 minute or 2 after the gas is stopped. The patient is then allowed to rest from 3 to 5 minutes, and a similar hyperpnea is again induced. Two such periods of hyperpnea constitute a treatment. This double inhalation is repeated at intervals of 3 hours during the waking hours and usually once or twice at night when the patient awakens. The administration of the gas is continued until the temperature becomes normal.

Immediate Effects of the CO_2 Inhalation. The inhalation of carbon dioxide gas was begun in most instances *within the first 48 hours after onset of symptoms.*

The following is the usual sequence of events when the gas is given: after the first few breaths the patient involuntarily coughs several times. After the administration of the gas is completed a severe paroxysm of coughing may appear, during which the patient brings up surprisingly large amounts of yellow pus.* Soon afterward he falls asleep, apparently in a state of exhaustion, but awakens later with a feeling of well-being and of being refreshed all out of proportion to the degree of illness which was present several hours before. From the time of the first inhalation of the gas the patients of their own accord state that they feel much better.

TABLE 4.—DURATION OF FEVER (DAYS) IN 46 PATIENTS TREATED WITH EARLY INHALATION OF CARBON DIOXIDE IN QUANTITIES SUFFICIENT TO CAUSE VENTILATION, OF WHOM 44 PATIENTS RECOVERED AND 2 DIED.

Days of fever.	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	14.
Broncho-pneumonia	2	7	8	5	3	0	3	1	0	2	0	1
deaths	0	0	1	0	0	0	0	0	0	0	0	0
Lobar	1	1	2	4	2	0	2	0	0	0	1	1
deaths	0	0	0	0	0	0	0	0	0	0	1	0
Total cases	3	8	10	9	5	0	5	1	0	2	1	2
Total deaths	0	0	1	0	0	0	0	0	0	0	1	2

Average days of fever: Bronchopneumonia, 4.3; lobar pneumonia, 5.2.

Appearance of Clinical Improvement. Within the first 24 to 48 hours most of the patients showed a marked decrease in toxicity, and by the time the fever abated they looked and felt well enough to get out of bed, even though the physical signs of the disease in the chest were still present and in some cases continued for 6 to 15 days after defervescence was completed. Although clinical improvement may thus appear very early, physical signs of resolution might not appear for from 3 to 5 days after the first adminis-

* This pus is, at first, viscid and thick, but later becomes thin and more liquid in consistency.

tration of gas. Figs. 1, 2 and 3 show typical temperature charts in bronchopneumonia and lobar pneumonia, treated with early inhalation of carbon dioxide.

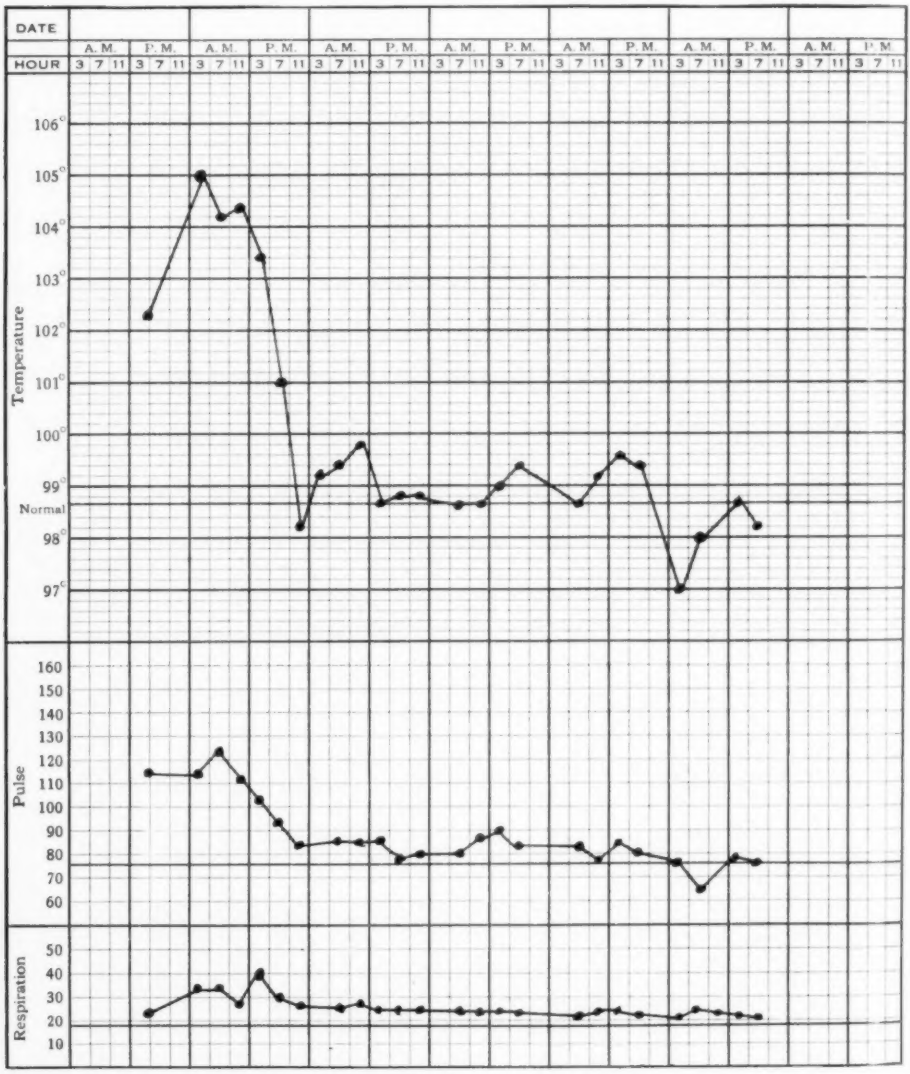

FIG. 3.—Case 21040. Male, aged 15; lobar pneumonia. Upper respiratory infection for 3 days prior to admission, when patient developed pneumonia. On examination: Temperature, 102.4° F. On admission, he showed cyanosis, diminished expansion at the right base with dullness; absent breath sounds and fine crackling râles. Roentgen ray examinations revealed infiltration at the base of the right lung. Treatment: Carbonic acid gas inhalations were started 12 hours after entry, and given every hour by day and every 3 hours at night. Crisis took place 12 hours after the therapy was commenced. Notes: Symptomatic improvement was noted on the second day. The chest was clear in 9 days.

Complications and Contraindications. Untoward results of the administration of the gas were noticed in 2 patients. In both instances it was noted that these patients developed a facies strongly resembling the mask facies of encephalitis and 1 of these patients complained of diplopia. In both instances, however, all symptoms and signs disappeared within the next 2 days and the patients appeared normal thereafter. The patient who developed a subjective diplopia suffered from a lobar pneumonia and received the inhalations at 2-hour intervals. The other patient was a very small woman who was receiving the gas at 3-hour intervals.

Two failures were observed in the entire adequately treated series (Group C). One was a patient with diffuse bilateral bronchopneumonia which involved most of both lungs. The defervescence did not occur as anticipated. The patient was extremely ill but she recovered. The second patient, who had a lobar pneumonia was the 81-year-old woman who also suffered from heart disease. One cannot say whether or not the administration of the gas played a rôle in these recoveries. However, the main contraindication for the use of carbon dioxide gas would appear to be in instances of patients suffering from myocardial insufficiency.

Some Reasons for Inadequate Therapy and Poor Results. This series[3] included patients whose ages ranged from 47 days (with recovery) to 89 years (with a death). The greatest source of error lies in the failure to continue the inhalation until a true hyperpnea takes place. The second source of trouble is the failure adequately to space the hyperpnea reactions to intervals of 3 to 4 hours. Poor results were commonly obtained in the use of carbogen gas (5% carbon dioxide in oxygen). This gas cannot be given in adequate concentrations by the open or drip method to produce the necessary ventilation, and if used at all, it must be given with a mask by the closed method as one does in administering an anesthetic gas. The greatest drawbacks in the use of carbogen are (1) the frequency of administration that is necessary and (2) the great expense involved.

In the authors' experiences, as well as those reported personally to them by other physicians, it was found that the inhalation of the gas cannot be given successfully to patients who suffer from myocardial insufficiency. Such patients develop a distressing dyspnea consisting of shallow rapid respiration which does not adequately ventilate the lungs.

Summary. In the observed cases of pneumonia here reported, the defervescence appeared in 87% of the patients within 1 to 7 days. The average duration of fever was 4.3 days for bronchopneumonia and 5.2 days for lobar pneumonia. The toxicity of the illness disappeared within 24 to 48 hours. The first administration of the gas caused a coughing reflex of severe nature after which copious amounts of purulent material were expectorated. Exhaustion and refreshing sleep followed. Resolution of the disease process appeared in from 3 to 5 days after the administration of the gas.

The physical signs in the chest persisted for several days after the temperature became normal. The mortality rate of the group treated by early inhalation of CO_2 was 4% as compared with 17% on the group receiving no CO_2 inhalations.

It must be emphasized here that these observations were made in patients in whom the disease was diagnosed, and the treatment begun in most instances within 48 hours after onset of the first symptoms.

Conclusions. 1. The administration of carbonic acid gas shortens the course of both bronchopneumonia and lobar pneumonia, particularly the former, the average days of fever being 4.3 days for bronchopneumonia and 5.2 days for lobar pneumonia.

2. The defervescence occurs rapidly in either type of pneumonia.

3. The mortality is definitely diminished and compares most favorably with that of other established methods of treatment.

4. The early administration of carbonic acid gas is a valuable therapeutic measure in the treatment of pneumonia.

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THE INADEQUATE TREATMENT OF EARLY SYPHILIS.

CLINICAL RESULTS IN 409 PATIENTS.

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PREVIOUS studies of the end results following the inadequate treatment of early syphilis have been based upon patients who returned to the clinic because of ailments due or thought by them to be due to their previous infection, or who were discovered when they returned for reasons unrelated to their earlier complaints. It is recognized that these patients include only a small proportion of individuals insufficiently treated for early syphilis, and that the ultimate outcome of the large majority who lapse before treatment is completed cannot be determined with any degree of accuracy. The most important reasons for this are: (1) While the average patient with a genital sore or a persistent skin eruption usually suspects he has syphilis, and may apply directly for treatment, he

is much less familiar with the manifestations of late syphilis, and if he becomes ill, may seek medical attention anywhere; (2) since the Wassermann test is not a routine procedure, unless he presents a classical picture of the disease in its late stages, or returns to the clinic or physician where he was first treated, the relation of his old infection to his presenting complaints may not be detected; and (3) many patients who remain symptom-free, or who develop benign skin or bone syphilis, never return for medical care.

It appeared, therefore, that a review of the patients coming to this clinic might throw some light on the ultimate outcome following inadequate treatment for early syphilis. The publicity of the Institute repeatedly stresses the necessity for continuous treatment, particularly of early syphilis. As a result many patients are examined who have no specific complaints, but who are interested in learning whether they have been cured or if further treatment is necessary. The difference between this material and that reported in other studies is in the inclusion of a large number of individuals who, remaining well, would probably not have given further thought to their infection had it not been forcibly brought to their attention.

Material and Methods. The material was obtained by reviewing all of the admissions during the period from January 1, 1933, to December 31, 1934. From these records a selection was made of all white male patients over 16 years of age, with a reliable history of acquired infection, who had received inadequate treatment for early syphilis, and who were examined at this clinic after an interval of at least 1 year from the last treatment. Patients were excluded who on reëxamination presented negative clinical and serologic findings but whose spinal fluid had not been analyzed. On the other hand, patients with serologic or clinical evidence of syphilis on reëxamination were included even though a spinal fluid examination had not been obtained. By inadequate treatment for early syphilis is meant the administration of less than 20 injections of a trivalent arsenical and of a heavy metal within a period of 1 year, this amount having been administered during the first 2 years following infection. A total of 409 patients were found to fulfill the above criteria, and it is on this group that the present report is based.

Evaluation of Treatment Results. In evaluating the final outcome, two classifications were employed, that is, "result satisfactory" and "result unsatisfactory." The latter group comprised those patients who developed clinical or serologic recurrences at any time following the institution of early inadequate therapy. The "result satisfactory" group includes patients observed for at least 1 year after the end of treatment, during which time no symptoms of syphilis developed and the blood serologic reaction was persistently negative. Moreover, all patients in this group had negative physical and spinal fluid examinations at the end of the year or thereafter.

In a few instances the X^2 test of homogeneity[7] has been employed to analyze the results statistically.

Comparative Results According to the Diagnosis at the Time Treatment Was Begun. Table 1 presents an analysis of the results of inadequate therapy according to the stage of the disease when treatment was started. The usual diagnostic classes are shown. In addition to these, there were 72 patients who received their first treatment in the primary stage, but who either had no Wassermann examination at the time or, if this was performed, its result could not be ascertained. These patients have been classified as sero-unknown primary syphilis. This group was included in the series in spite of the uncertainty regarding the Wassermann reaction, because subsequent observations revealed that the large majority, that is, 64 (89%) developed clinical or serologic evidence of syphilitic infection.

TABLE 1.—RESULTS ACCORDING TO STAGE IN WHICH TREATMENT WAS BEGUN.

Result.	Sero-negative primary.		Sero-positive primary.		Sero-unknown primary.		Total primary.		Secondary.		Early latent.*		Total.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Satisfactory	17	80.9	69	37.5	8	11.1	94	33.9	34	31.2	6	26.1	134	32.8
Unsatisfactory	4	19.1	115	62.5	64	88.9	183	66.1	75	68.8	17	73.9	275	67.2
Total	21	100.0	184	100.0	72	100.0	277	100.0	109	100.0	23	100.0	409	100.0

* First 2 years of infection.

It is seen that 17 (80.9%) of the 21 patients first treated in the seronegative primary stage had a satisfactory outcome. The frequency of satisfactory results in the seronegative primary patients was statistically significantly greater than that in each of the other 3 groups, but the difference between any 2 of the latter 3 was not statistically significant, probably due to insufficient numbers. This comparison does not include the sero-unknown primary group. However, the results show a progressive decrease in the incidence of arrest and cure, and a progressive increase in the incidence of recurrences, with increasing intervals from the date of infection to the beginning of therapy. This finding is, of course, not novel, since it is now an accepted principle in the modern treatment of syphilis. What is deserving of special comment, however, is the fact that this result occurred even though all patients received inadequate therapy. The data of Moore and Kemp,[6] when recalculated on the basis of inadequate treatment, point to a similar conclusion. It is apparent that whether or not a patient expects to or can continue throughout a prescribed régime of adequate therapy, the earlier the diagnosis is made and treatment instituted, the more favorable is his prognosis.

Comparative Results With Continuous and Discontinuous Treatment Systems. Continuous treatment is here defined as the uninterrupted administration of an arsenical or a heavy metal or both. Patients whose treatments did not fall into this category received "discontinuous" treatment. Subdivisions into intermittent and irregular treatment schedules were not attempted, since by so doing the size of the resulting classes would have been diminished, and the significance of the findings decreased.

The influence of continuous and discontinuous treatment régimes on the ultimate outcome is shown in Table 2. Satisfactory results were obtained in 78 (42.2%) of the continuous treatment group, as compared with only 56 (25%) of patients whose treatment system was discontinuous; the difference between these two values is statistically significant. The superior results of continuous treatment are evident regardless of the stage of the disease when therapy was begun. Statistical analysis also indicates that a significantly larger proportion of patients in the satisfactory outcome group (78 out of 134, or 58.1%) received continuous treatment than the comparative proportion in the unsatisfactory result group (107 out of 275, or 38.9%). On the basis of these findings, a patient with early syphilis should be placed on a continuous therapy régime, for even though he should lapse before receiving adequate treatment, his chances for an ultimate satisfactory outcome are greater under such a régime than they would be under any other system.

TABLE 2.—RESULTS ACCORDING TO TYPE OF TREATMENT—CONTINUOUS OR DISCONTINUOUS.

Treatment system.	Result	Seronegative primary.		Seropositive primary.		Serounknown primary.		Total primary.*		Secondary.		Early latent.*		Total.	
		No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Continuous	Satisfactory	14	93.3	41	43.6	5	21.7	60	45.4	13	33.3	5	35.7	78	42.2
	Unsatisfactory	1	6.7	53	56.4	18	78.3	72	54.6	26	66.7	9	64.3	107	57.8
	Total	15	100.0	94	100.0	23	100.0	132	100.0	39	100.0	14	100.0	185	100.0
Discontinuous	Satisfactory	3	50.0	28	31.1	3	6.1	34	23.4	21	30.0	1	11.1	56	25.0
	Unsatisfactory	3	50.0	62	68.9	46	93.9	111	76.6	49	70.0	8	88.9	168	75.0
	Total	6	100.0	90	100.0	49	100.0	145	100.0	70	100.0	9	100.0	224	100.0
Total		21	100.0	184	100.0	72	100.0	277	100.0	109	100.0	23	100.0	409	100.0

* First 2 years of infection.

Results According to Amounts of Treatment. In grouping the treatment schedules so as to indicate the number of doses without regard to their continuity or lack of continuity, "much" here signifies 15 or more injections when referring to an arsenical, and 10 or more when referring to a heavy metal. "Little" indicates less than these

amounts. In the text the first of the two adjectives refers to arsenical and the second to heavy metal. Thus "much-little" signifies much arsenical, little heavy metal.

The clinical results according to varying amounts of inadequate treatment are shown in Table 3, which is based on the entire group without regard to the stage of infection when therapy was instituted. The comparative values for the different diagnostic classes were identical with those shown in the table, and for this reason only the summated findings are presented.

TABLE 3.—RESULTS ACCORDING TO AMOUNTS OF TREATMENT.

Result.	Little-little.		Little-much.		Much-little.		Much-much.		Total.	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Satisfactory	58	26 7	32	32 7	23	44 2	21	50 0	134	32 8
Unsatisfactory	159	73 3	66	67 3	29	55 8	21	50 0	275	67 2
Total . . .	217	100 0	98	100 0	52	100 0	42	100 0	409	100 0

See text for definition of terms "little-little," "little-much," etc.

Treatment successes ranged from a low of 58 (26.7%) of 217 patients receiving little-little therapy, to a high of 21 (50%) of 42 receiving much-much therapy. The difference between these two values is highly significant statistically. Little-little therapy was represented in a statistically significantly smaller proportion of treatment success than treatment failure cases. Thus 58 (43.3%) of the 134 patients in the satisfactory outcome group received this amount of treatment as compared with 159 (57.8%) of the 275 in the treatment failure group. Moreover, the frequency of cases in the satisfactory outcome group given much-much therapy (21 out of 134, or 15.7%) was significantly greater than the frequency of patients in the unsatisfactory outcome group who had been treated with similar amounts of an arsenical and of a heavy metal (21 out of 275, or 7.6%). The evidence thus indicates that even though treatment may be inadequate according to the standards now generally accepted, the incidence of successful results increases with increasing amounts of therapy.

Analysis of Unsatisfactory Results. The patients who experienced an unsatisfactory outcome were classified as follows: (1) Wassermann recurrent latent syphilis. (2) Early infectious relapse. (3) Central nervous system syphilis. (4) Cardiovascular syphilis. (5) Late benign and visceral syphilis.

Table 4 presents an analysis of the observed recurrences based on varying amounts of treatment for early syphilis. Summating

the three types of late syphilis having serious import, that is, neurosyphilis, cardiovascular syphilis, and late benign and visceral syphilis, the combined incidence of these recurrences in the different treatment groups was as follows: little-little, 50.7%; little-much, 36.7%; much-little, 32.7%; and much-much, 33.4%.

TABLE 4.—ANALYSIS OF RECURRENCES ACCORDING TO VARYING AMOUNTS OF TREATMENT.

Treatment	Little-little		Little-much		Much-little		Much-much		Total	
No. of patients	217		98		52		42		409	
	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.	No.	Per cent.
Wassermann recurrence	52	23.9	31	31.6	13	25.0	4	9.5	100	24.5
Early infectious relapse	8	3.7	3	3.1	..	..	4	9.5	15	3.7
Central nervous system	72	33.2	22	22.4	16	30.8	11	26.2	121	29.6
Cardiovascular	26	12.0	11	11.2	..	..	3	7.2	40	9.8
Late benign and visceral syphilis	12	5.5	3	3.1	1	1.9	..	..	16	3.9
Total recurrences	170	78.3	70	71.4	30	57.7	22	52.4	292	71.4
Cases with 1 recurrence	159	73.3	66	67.3	29	55.8	21	50.0	275	67.2
Cases with more than 1 recurrence	11	5.1	4	4.1	1	1.9	1	2.4	17	4.2

An analysis of the incidence of these three serious late sequelæ according to the stage of the disease when treatment was initiated showed the same comparative results for each type of systemic involvement. In each case the incidence was lowest in the seronegative primary group, much higher in the seropositive primary group, and still higher in secondary syphilis patients. The frequency of each of these three recurrences then fell off slightly in the group with early latent syphilis. These findings are well shown by the combined values: seronegative primary, 9.5%; seropositive primary, 34.2%; secondary, 45.9%; and early latent, 39.1%.

The most important type of unsatisfactory result from a public health viewpoint is that of infectious relapse. The incidence of this condition was 3.7%, which is much lower than the 13.3% frequency observed by Moore and Kemp in their inadequately treated group, and also lower than the 13.1% incidence among inadequately treated patients in the Coöperative Clinical Group material.[5] It is of interest to note also that the percentage of neurosyphilis is appreciably less than that reported by Kemp and Menninger[4] in inadequately treated patients (43.4%) and in untreated patients (52.6%). Since only 56 of the 100 patients with Wassermann recurrent latent syphilis had a spinal fluid examina-

tion in all probability the 29.6% represents the minimum of neurosyphilis. By the same token, the percentage of latent syphilis is probably lower than that shown by our figures. The incidence of cardiovascular syphilis among these patients is slightly lower than that observed by Kemp and Cochems.[3] It seems probable that the incidence of each of these recurrences is lower than that reported by other investigators because of the inclusion in this material of a large group of symptom-free patients who ordinarily do not report to the physician or clinic for reëxamination.

The Satisfactory Result Group. Table 5 represents an analysis of the 134 patients classified as "result satisfactory." Every patient included in this group had a negative spinal fluid examination. Thirty-four (25.3%) were observed for periods ranging from 1 to 4 years after the last treatment; 58 (43.3%) of the 134 patients were observed for from 10 to 15 years and more after the last treatment, the longest interval being 30 years. Of this group, 32 (55.2%) had negative Roentgen ray and electrocardiographic examinations.

TABLE 5.—THE INTERVAL BETWEEN LAST TREATMENT AND FINAL OBSERVATION IN 134 SATISFACTORY RESULT CASES.

Interval in years.	1	2–4	5–9	10–14	15+	Total.
No. of cases	5	29	42	31	27	134
Per cent of total	3.7	21.6	31.3	23.1	20.2	100.0
Negative Roentgen ray and electrocardiogram	2	7	23	18	14	64
Negative provocative	1	11	16	11	8	47

The first 2 years following cessation of treatment is the critical period so far as infectious relapses are concerned. In the Coöperative Clinical Group material,[1] 91% of all infectious relapses occurred during this interval. The comparative value obtained in the present study was 86.7%. The great majority of patients in the "satisfactory result" group were, therefore, well outside this danger zone, for 117 (87.3%) had been observed for periods exceeding 2 years after the cessation of treatment.

The probability that any of these 117 patients might later develop central nervous system involvement is exceedingly remote, for it is now recognized that a negative spinal fluid examination 2 years or more after infection assures the patient of subsequent normal spinal fluid findings, except under very unusual circumstances. The situation is quite different with respect to cardiovascular syphilis. A negative cardiovascular examination is no guarantee against future involvement of this system. In the Coöperative Clinical Group material of 186 cases of uncomplicated aortitis where the duration of infection was known, there were 90% in which the process had developed to the point of detection later than 5 years from infection.[2] Aortic regurgitation was noted most frequently in the period 20 to 30 years from infection. It is thus apparent that, excluding late skin and bone tertiarism, the most serious danger confronting the satisfactory result group is the possibility of subsequently developing cardiovascular recurrence.

However, the chances are overwhelmingly in favor of a continued state of health in patients who are clinically and serologically negative 5 years and more after the cessation of treatment, and such patients comprised 74.5% of our group.

The individual who maintains clinical and serologic negativity for varying periods following the last treatment is naturally desirous of knowing whether he is likely to continue so throughout life. This information is highly desirable to the clinician, also, especially with reference to the patient known to have been inadequately treated for early syphilis. Shall further treatment be instituted as an added protection against late serious recurrences, or do the physical discomfort, financial stress, and even danger of antisyphilitic measures to the patient outweigh any possible benefits he may derive? With this question in mind, a selection was made of all patients who were subjected to a complete reëxamination one or more years following a negative physical, blood and spinal fluid examination. Only 43 such cases were found. In each instance the reëxamination conducted from 1 to 25 years after the first negative survey was also negative, and each of these 43 patients is included in the satisfactory result group. These findings indicate the comparative security which a patient with negative findings may enjoy, but it should be emphasized that the small size of the group prevents any sweeping generalizations.

Discussion. The observation that 134 (32.8%) of the patients in this series achieved a satisfactory result in spite of early inadequate treatment is deserving of special comment. The question arises whether this percentage represents a fair approximation of the satisfactory result cases in a large population of inadequately treated patients. At the outset it must be admitted that the asymptomatic patient generally has no reason to enter a hospital, so that reports emanating from such institutions do not give a true picture of the situation. This is a valid objection to the findings of Stokes and Des Brisay,[8] who observed clinical, spinal fluid and serologic negativity in only 17 (8.4%) of 178 inadequately treated syphilitics. Their result is based on a selected group of individuals, that is, those who reported to a hospital for the relief of symptoms, the syphilitic infection being discovered through routine diagnostic procedures. Is our material characterized by a bias in the opposite direction, and does this account for our higher percentage of satisfactory results?

It is our impression that this is not the case. In the first place, it will be recalled that the series does not include a large number of patients who were clinically and serologically negative, but whose spinal fluid had not been examined. Had this examination been conducted, a large majority would have been found to have negative spinal fluids, and this would have placed them in the satisfactory result group. This alone, other factors being equal, would have produced an incidence of satisfactory results higher than that reported.

Moreover, each patient in the satisfactory result group came to

the clinic because of his own knowledge of an antecedent infection, and not because he was compelled to seek relief for distressing symptoms. Such individuals are generally not included in hospital statistics because they are not components of the average hospital population. The objection may be raised that if it is true that a hospital group does not consist of a representative sample of asymptomatic syphilitics, by the same token it is comprised of a higher proportion of the general population of patients with symptomatic recurrence than is found in our material. This objection is based on the premise that more patients with serious recurrences are seen in the hospital than in an ambulatory clinic. While no actual data can be given on this point, attention should be called to the fact that many of our symptomatic patients were hospitalized on our recommendation, and furthermore, that many patients returned to us for follow-up care after their acute siege in a hospital had subsided. With the exception of a very small percentage of individuals who are rushed to a hospital as a result of sudden crucial symptoms, there to die, the clinic at one time or another probably sees the great majority of patients with serious symptomatic recurrence.

In conclusion, it should be emphasized that these results are not to be interpreted as a brief for inadequate treatment. The recommendations of the Coöperative Clinical Group and of the Health Organization of the League of Nations should be rigorously followed, and any physician responsible for the inadequate treatment of early syphilis is remiss in his duty to both patient and public.

Summary. A study was made of the outcome in 409 patients who had received early inadequate treatment for syphilis. Patients were classified as "result satisfactory" if they presented no evidence of syphilis as determined by clinical, serologic and spinal fluid tests one year or more after the last treatment; and as "result unsatisfactory" if they developed clinical, serologic, or spinal fluid signs of syphilis at any time following the cessation of treatment.

With regard to the diagnosis when treatment was begun, the highest proportion of satisfactory results was noted in the seronegative primary stage.

A significantly higher incidence of satisfactory results was observed among patients who had received continuous treatment than in those treated by other systems.

Much arsenical was defined as 15 or more injections of a trivalent preparation and much heavy metal as 10 or more injections of bismuth or mercury. Treatment successes were lowest in the group receiving less than these amounts of both drugs, and highest in those treated with these amounts or more.

Central nervous system syphilis comprised the largest proportion of late relapses. Wassermann recurrent late syphilis had a slightly lower incidence and cardiovascular syphilis still lower. Early infectious relapse and late benign and visceral syphilis had an equal and also the lowest incidence.

The 134 patients classified as result satisfactory were followed for from 1 to 30 years after the last treatment; 117 (87.3%) of these had been observed for periods longer than 2 years after the cessation of specific medication. It was pointed out that the most serious danger confronting these patients was the possibility of subsequently developing cardiovascular recurrence.

Of the 409 patients comprising this study 32.8% achieved a satisfactory result. An analysis was made of the sampling factors which might have been influential in producing this proportion of favorable results. It appeared that this value probably represents a fair approximation of the incidence of satisfactory result cases in a large population of patients inadequately treated for early syphilis.

It was emphasized that although inadequate treatment does produce a certain proportion of successful results, adequate treatment schemes as recommended by the Coöperative Clinical Group and by the Health Organization of the League of Nations should be rigorously followed in the management of early syphilis.

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AN EXPERIMENTAL STUDY OF THE VARIATIONS IN THE PRODUCTION OF VISUAL DISTURBANCE BY CERTAIN NEW CINCHONA DERIVATIVES.

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The frequency of visual damage following therapeutic use of certain cinchona alkaloids, especially of ethylhydrocupreine, is attested by a large number of case reports, groups of clinical cases

and experimental data in animals,[9] as well as by personal experience. The pathologic lesions responsible for loss of vision is recognizable both by means of the ophthalmoscope and by microscopic tissue section, and has been adequately described.[4] There is a fair amount of evidence pointing toward the factor of individual idiosyncrasy.[5] However, the exact mechanism producing the lesion is not agreed upon. It is believed by some to be direct toxic action on the retinal cells but other evidence points toward primary spasm of retinal arteries resulting either from direct action of the compounds as vasoconstrictors, or, as recently suggested by Wolff,[11] the retinal vascular spasm may be the result of depressed tissue oxidation.

During the course of a more extensive experimental and clinical investigation of a large number of cinchona alkaloids,*[6] an attempt has been made and is herewith reported to estimate the toxicity to the visual apparatus of certain of these alkaloids which have a high pneumococcidal power and a general toxicity low enough to justify consideration of their clinical use in pneumococcal pneumonia.

Experimental. The work of Smith and Fantus[10] suggested that in the perfused peripheral vessels of the frog ethylhydrocupreine possessed greater vasoconstricting properties than quinine. Using the alkaloids in concentrations approximating 1:2000 (M/648, monohydrochloride), the only definite finding so far in the present work is that peripheral vasoconstriction in the frog appears to be a general reaction of cinchona bases. It has been obtained with quinine, apocupreine (apoquinine), ethylapocupreine, ethylhydrocupreine and its d-rotatory isomer ethylhydrocupreidine, and with hydroxyethylapocupreine. It seems not invariably to be obtained with any of these substances. Thus, with hydroxyethylapocupreine, of 12 preparations perfused as indicated, 4 did not show definite persistent constriction; with ethylhydrocupreine the corresponding figures were 4/10, with quinine 1/12. The Ringer formula was NaCl 6.5, KCl 0.14, $CaCl_2$ (anhydrous) 0.24, $NaHCO_3$ 0.2 gm. per liter. The cannula insertion was through ventricle into bulbus. It may be that under some set of conditions this method might prove of use for attack on the problem of cinchona amblyopia, but at present it appears less promising than the direct method.

A direct attack on the problem of cinchona amblyopia was made by eye examination following injection of quinine, ethylapocupreine and ethylhydrocupreine subcutaneously in the frog.[8] These doses were 0.01 to 0.02 cc. M/20 dihydrochloride per gram and were definitely in the lethal range. No changes definitely attributable to the injections were noted in the eye grounds.

Preliminary observations were then made on dogs injected intraperitoneally with ethylhydrocupreine. It was not found possible to give doses exceeding 84 mg. (expressed as dry base) per kg. by this route without fatality, and eye changes were not marked (Table 1). Much larger doses were, however, tolerated by subcutaneous injection. A mid-dorsal, rather than a flank, site was chosen to avoid the chance of direct penetration of solution into the body cavity, with possible alteration of rate of absorption and visceral damage.[1] The plan, therefore, gradually developed of giving

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a single mid-dorsal subcutaneous injection of a large dose, 0.25 to 0.50 mg. mol. dihydrochloride per kg. The surviving dogs were observed for varying periods, up to 49 days, then killed. The eyes were removed at once and fixed, one in Zenker's solution and one in the following mixture: absolute alcohol by volume, 6 parts; chloroform, 3 parts; glacial acetic acid, 1 part. The Zenker-fixed tissue was stained with hematoxylin and eosin, the specially fixed tissue with toluidine blue and phloxine, both from paraffin-embedded material.

Ophthalmoscopic Findings. Minor grades of visual damage were naturally not certainly detectable by ophthalmoscopic examination. Dogs with serious visual disturbance generally showed pallor of the disc at the time or within a few days later. Pupils of such dogs were usually dilated and responded sluggishly to light. Retinal arterial constriction was difficult to assess.

Microscopic Findings (Table 1). These were identical with those of Forster[4] and previous workers referred to by him.

TABLE 1.—EFFECTS OF CINCHONA BASES ON DOG EYE.

Dog No.		Dose, Mg., dry base/K.	Visual disturbance.	Ophthalmoscopic change.	Microscopic change.	Days after injection.
2*	Ethylhydrocupreine	42*	None	Doubtful	Slight	1
8*	Ethylhydrocupreine	42*	Slight	Slight	Slight	5
9*	Ethylhydrocupreine	42*	None	Doubtful	Slight	5
3*	Ethylhydrocupreine	63*	None	Doubtful	Slight	1
6*	Ethylhydrocupreine	37 x 7 daily	None	Slight	Doubtful	8
11	Ethylhydrocupreine	170	Blind 5th day	Marked	Marked	41
13	Ethylhydrocupreine	170	Blind 1st day	Marked	Marked	2
10	Ethylhydrocupreine	212	Blind 2d day	Marked	Marked	7
16†	Ethylapocupreine	169	Blind 1st day	Marked	Marked	49
17	Quinine	162	Blind 2d day	Marked	Marked	41
C-3	Hydroxyethylapocupreine	88	None	None	None	28
27	Hydroxyethylapocupreine	132	None	None	None	17
28	Hydroxyethylapocupreine	132	None	None	None	10
C-2	Hydroxyethylapocupreine	132	None	None	None	28
26	Hydroxyethylapocupreine	177	None	None	None	17
C-1	Hydroxyethylapocupreine	177	Questionable	None	Very slight	28
30	Hydroxyethylapocupreine	177	None	None	None	9
31	Hydroxyethylapocupreine	177	None	None	None	14
32	Hydroxyethylapocupreine	177	None	None	None	14
33	Hydroxyethylapocupreine	177	None	None	None	14
37	Hydroxyethylapocupreine low rotating fraction	100	None	None	None	14
35	Hydroxyethylapocupreine low rotating fraction	167	None	None	None	14
23‡	Quinidine	81	None	Doubtful	Very slight	6
24	Isopropylapocupreine	132	Blind 6th day	Marked	Marked	14
25	Isopropylapocupreine	176	Blind 2d day	Marked	Marked	14
34	Butoxyethylapocupreine	145	None	None	None	14
38	Butoxyethylapocupreine	145	None	None	None	6
36§	Butoxyethylapocupreine	194	..	..	None	8

N.B. "C" dogs injected in Laboratory of Pharmacology, University of Chicago.

* Intraperitoneal injection; the rest subcutaneous.

† Dogs 14 and 15 not notably affected by same dosage; observed 5 and 6 days respectively. Eyes not removed.

‡ Dog 22 killed by same dosage.

§ Dog 36 developed distemper and only microscopic observations were made.

1. Eyes from 10 control dogs showed normal retina, choroid and sclera.

2. No visible change in the blood-vessels was seen in *any* section of eye of *any test* or *control* animal. In the test animals, the changes were confined to the retina proper.

3. In those test animals showing changes, destruction of cells of the ganglion layer predominated, the number of destroyed cells varying from a few to all ganglion cells. In those dogs allowed

to survive for ten days or more, any ganglion cells remaining were in a state of good preservation. Dogs killed before the tenth day showed, in addition, some edema of retina and an occasional lymphocyte or polymorphonuclear leukocyte. Occasional changes in the cells of the bipolar layer were seen in the more severely damaged eyes.

Other Observations. Local necrosis, which appears to be a general reaction to subcutaneous injection of cinchona bases (Dawson and Bodansky),[2] was noted rather frequently in the form of a sloughing of the skin at the site of injection. It seems to have nothing to do with eye changes, and does not appear to influence the general health. Dogs which following injection presented persistent drug toxicosis or were for any other reason in poor condition, were sacrificed to prevent postmortem eye changes before fixation. Some of the periods of observation were, therefore, rather short. In Dogs 11 and 17 there seemed to be some possible lessening of the amblyopia 24 and 35 days, respectively, after injection.

Cinchona bases seem to be well absorbed from subcutaneous injection in spite of the possibility of local necrosis. Thus, Dogs 19, 20 and 21 were all killed by a dose of 101 mg. quinidine base per kg., M/8 solution in the calculated amount of standard HCl; Dogs 12 and 18 were similarly killed by M/4 solutions of ethylhydrocupreine and quinine, the doses of anhydrous base being 170 and 162 mg. per kg., respectively.

Statistical Calculation of Significance of Results. If we arrange two groups of dogs on the basis of probable essential difference in chemical formula and approximately similar handling, we have in Group 1 Dogs 11, 14, 15, 16, 17, 24, 25, receiving cinchona alkaloids of abbreviated formula RO.B, where B stands for "base" and RO for alkoxy side chain; in Group 2, Dogs C1, C2, 26, 27, 28, 30, 31, 32, 33, 35, formula HORO.B for hydroxy-alkoxy side chain. The results may be set up as in Table 2.

TABLE 2.—EFFECT OF INTRODUCTION OF BETA HYDROXYL RADICAL INTO ALKYL OF CINCHONA ALKOXY SIDE CHAIN ON TENDENCY TO PRODUCE BLINDNESS IN DOGS.

Group.	Side chain.	Dosage mg. per kg.	Observed for days.	Blind.	Not blind.	Total.
1	RO	132–176	5 or more	5	2	7
2	HORO	132–177	9 or more	0	10	10
			Total	5	12	17

While the numbers involved are small, they are yet obviously suggestive of substantially less danger of visual damage from hydroxyethylapocupreine than from the group "RO" alkaloids. Calculation by the "Exact" method of Fisher,[3] Section 21.02, shows that the probability of such a set of results being due to chance is only 1 in 294.

Discussion. It may seem surprising that there should be any difference in action on the retina of two substances so closely alike in chemical formula as ethyl- and hydroxyethylapocupreine. Young

and Loevenhart,[12] however, noted the production of optic lesions in the rabbit by organic arsenicals with an amino or substituted amino group in the para position to the arsenic, but not with the amino or substituted amino group in the ortho or meta position.

The results of the "dog test" described have already been utilized.[7] Owing to its serious eye effects in dogs, isopropylapocupreine was excluded from clinical trial while hydroxyethylapocupreine, owing to its lack of such effects in dogs, has been introduced. Both of these drugs previously had appeared desirable on the ground of *in vitro* and *in vivo* pneumococcicidal activity displayed by the methods used by Maclachlan, Permar, Johnston and Kenney.[6] While further work may cause a revision of opinion, this test seems likely to open up an avenue of approach somewhat safer than any previously available in the field of chemotherapy of pneumonia.

Summary. 1. An effort has been made to develop a method for the estimation of the property of visual damage possessed by certain cinchona alkaloids which are under investigation as to their possible therapeutic use in pneumococcus pneumonia.

2. Results of perfusion experiments in the frog with a number of cinchona alkaloids suggested that under the conditions used, peripheral vasoconstriction is a general reaction of cinchona bases. For attack on the problem of cinchona amblyopia this method appears at present less promising than the direct method.

3. Observation and histologic study of the eyes of dogs subcutaneously injected with large doses of these alkaloids indicate a distinct difference in their behavior with regard to retinal damage. The ganglionic layer was found damaged by ethylhydrocupreine, ethylapocupreine, isopropylapocupreine, and quinine. Comparable dosage with hydroxyethylapocupreine in 10 dogs caused no demonstrable damage. The difference in results appears to be statistically significant and coincides with clinical observations in man to be reported at a later date.

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SOMATIC PHENOMENA IN PSYCHONEUROSES.

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Although the scientific method (cause-effect) is by convention employed in most medical research, certain difficulties in the study of psychoneuroses preclude its employment there. First of all, despite the observation of Pavlov[7] and his pupils[8] of psychoneurosis-like states in animals used for the study of conditioned reflexes, it may be said that a true psychoneurosis is peculiar to man. Second, our present day concept of the pathogenesis and etiology of psychoneurosis makes it obvious that its deliberate production in any man is unwarranted. Hence, any study of the psychoneuroses must be made as they spontaneously present themselves. In making such a study one may describe and classify the observed phenomena, reason slowly backwards from effect to cause and then direct therapeutic efforts towards the alteration of the hypothesized cause. If therapeusis of this type results in cure in a sufficient number of instances, one may infer that the hypothesis is established.

The diagnosis of psychoneurosis is made always by exclusion. It is necessarily preceded by a thorough physical examination supplemented by any indicated studies, and if the latter prove negative, thus ruling out organic disease, one is justified in surmising that psychic factors are responsible for the derangement in function or for the symptoms of which complaint is made. The probabilities of the correctness of this surmise becomes even greater, if emotional conflicts, unhappiness and the like are found in the patient's history. If a therapeutic attack upon these emotional conflicts results in a restoration to normal function and a disappearance of symptoms, the probablity of the validity of the cause—effect reasoning process becomes greater still. Certainty is attained, however, only after one has studied a sufficiently large series of cases to rule out the possibility of fallacy in the inductive process.

The foregoing suggests some of the pitfalls lying ahead of one who attempts to study any aspect of the psychoneuroses. Such study can be made only by the employment of effect—cause reasoning upon the phenomena observed and by the employment of the therapeutic test upon the hypothesized cause. This method has been employed throughout the present study, and we have endeavored to bear in mind its inherent limitations.

The material for this study consisted of a group of 20 patients on whom the diagnosis of psychoneurosis was made after a careful history and physical examination supplemented by any indicated tests had excluded organic disease; 11 of these patients were women; 9 men. Their average age was 29 with variations between 24 and 32.

The presenting symptoms which occurred most frequently are shown in Table 1

TABLE 1.—PRESENTING SYMPTOMS IN 20 PSYCHONEUROTIC PATIENTS.

	Per cent.		Per cent.
Fatigue	90	Dyspnea	70
Digestive complaints	90	Headache	70
Excessive perspiration	90	Precordial discomfort	60
Coldness of extremities	90	Insomnia	60
Tachycardia	80		

The physical examination supplemented by laboratory studies revealed but slight variation from the normal average. Those findings deserving special mention are shown in Table 2.

TABLE 2.—OBJECTIVE FINDINGS IN 20 PSYCHONEUROTIC PATIENTS.

Low blood pressure	100	Lymphocytosis (above 35%)	85
Sugar tolerance definitely increased (low curve)	90	Low basal metabolism (below −5)	85
Moist skin	85	Coldness of extremities	75
Tenderness over colon in L. L. Q.	85	Cyanosis or "marbling" of extremities	70

Further evidence of similarity in these patients became manifest when attention was focussed upon the psychic background. All were unhappy; all were dissatisfied with life. However, we paid little attention to this condition at the time, for we felt that the psychic situation would clear up when the physical symptoms had disappeared.

At first, therefore, our endeavors were confined to explaining and treating the disorder on a purely physical basis. The most probable source of trouble at first was thought to lie in some one of the ductless glands. A therapeutic test was made with thyroid; but although the basal metabolic rate was raised to the normal level, little improvement was experienced by the patients. Indeed most of them were irritable and apprehensive in consequence of the treatment. Pituitary preparations were next tried, but without appreciable benefit. While these therapeutic tests were taking place, it was noted that the physical signs above referred to, were almost without exception the reverse of those described by Cannon[1] in his studies on the responses of animals to emotional stimuli and ascribed by him to generalized excitation of the sympathetic division of the autonomic nervous system. Throughout this paper, the division of the autonomic nervous system into sympathetic and parasympathetic is understood, as made by the pharmacologist rather than by the anatomist. The pharmacologist regards fibers stimulated by pilocarpine and paralyzed by atropine as parasympathetic; those stimulated by adrenalin as sympathetic. The anatomist regards fibers originating in the thoracic and lumbar regions of the cord, as sympathetic; in the brain stem and sacral region of the cord, as parasympathetic. A régime, therefore, was instituted to overcome this condition of autonomic imbalance. Cold baths, relatively small meals of easily digested food, moderate exercise and the use of drugs such as epinephrine, ephedrine and atropine were among the measures employed singly or collectively in the treatment of these

patients. There was no doubt that some of the patients were cured by these procedures, for the symptoms disappeared, the abnormalities revealed on physical examination or by the use of laboratory tests, were replaced by normal findings, and the patients expressed themselves as satisfied with the outcome. The results of treatment on laboratory manifestations are shown in Table 3.

TABLE 3.—RESULT OF PHYSICAL TREATMENT ON LABORATORY MANIFESTATIONS (8 CASES).

	Before treatment.	After treatment.
1. Blood pressure:		
Maximum	108/70	124/80
Minimum	88/54	110/72
Mean*	96/64	114/72
2. Basal metabolic rate:		
Maximum	−2	+10
Minimum	−22	−4
Mean*	−15	+3
3. Lymphocyte percentage:		
Maximum	46	35
Minimum	34	28
Mean*	40	32

Blood sugar tolerance:

	Fasting.	30 mins.	60 mins.	90 mins.	Fasting.	30 mins.	60 mins.	90 mins.
Maximum	84	98	122	100	106	158	140	122
Minimum	76	102	110	68	90	108	135	92
Mean*	79	105	110	86	97	136	129	101

* The arithmetical mean of 8 cases.

In view of the fact that certain patients continued to have symptoms, although the physical signs and laboratory tests had reverted to normal following the institution of the régime mentioned above, it was decided to investigate further the rôle played by psychic factors. When this was done, it was quickly ascertained that patients very often complain of the physical symptoms of an emotional reaction, while they withhold the story of emotional strain. Basically, these patients showed a common psychic pattern. All were faced by situations which were disliked, which were intolerable, and which could not be altered. Indeed, each one rebelled against the established order of things in a matter which was, for him, unchangeable. In a measure, each one of them rebelled against himself or, at least, against the inevitability of his own limitations, for the attainment of every objective is conditioned by an individual's capacities. Where one recognizes that one's objectives are unattainable, wisdom, of course, demands that one's objectives be changed. Our patients were unfortunate in that they either could not or would not alter their objectives, even in spite of the fact that they realized the impossibility of attaining them. The task of psychotherapy was, therefore, to assist them to do this. In brief, our method of treatment consisted in a thorough mental catharsis for the patient (although not as complete as that employed by a psychoanalytic school) and then in assisting him to re-synthesize his experience so that he could, if he so chose, alter the objectives of his life. The results were so gratifying in the cases in which

it was used in conjunction with physical methods of treatment, that it was decided to try the effect of psychotherapy alone on patients with findings similar to those mentioned above. Our astonishment was great in learning that treatment of this type supplemented by no physical measures whatsoever, was followed by a disappearance of symptoms, a return of physical signs and laboratory tests to normal and a restoration of the patient to health both mental and physical. The results of treatment on the laboratory manifestations in patients of this group are given in Table 4.

TABLE 4.—RESULTS OF PSYCHOTHERAPY ON LABORATORY MANIFESTATIONS (20 CASES).

1. Blood pressure:									
Maximum				112/60				138/88	
Minimum				84/44				102/54	
Mean*				98/62				124/80	
2. Basal metabolic rate:									
Maximum				−3				+16	
Minimum				−21				−8	
Mean*				−11				+2	
3. Lymphocyte percentage:									
Maximum				53				39	
Minimum				33				28	
Mean*				41				29	
4. Blood sugar tolerance:									
	Fasting.	30 mins.	60 mins.	90 mins.	Fasting.	30 mins.	60 mins.	90 mins.	
Maximum	90	160	132	108	96	164	128	90	
Minimum	84	108	108	92	94	108	120	102	
Mean*	81	110	121	106	99	131	116	113	

* The arithmetical mean of 20 cases.

Comment. The observations recounted above lead naturally to many questions, to no one of which a final answer can be given at the present time. Some of these questions have proved to be particularly fascinating, and an effort will be made to suggest answers which fit in with the remainder of our present-day knowledge. What is the fundamental nature of the physical disturbance? Can this physical disturbance be produced by both physical and psychic causative factors? How can these observations be reconciled with those of Cannon in his studies on the emotional reactions in lower animals? Why is this symptom complex observed only in the young?

Light may be thrown on the answer to the first question by recounting the studies of the physiologist and pharmacologist. Indeed our first clue to the nature of the physical disturbance came when we noted that this was the reverse of that described by Cannon[1] in the lower animals. The physical disturbance in our patients was likewise the reverse of the change produced by adrenalin.[2] On the other hand, it was very similar to that produced by pilocarpine,[2] muscarine[2] and choline in the animal. While the two first named substances are not to be found in the body, choline and its esters are present there in at least small quantities. The action of this substance has been studied rather exhaustively by Hunt and Taveau,[5] Dale,[3] Feldberg and Gaddum,[4] Loewi and Navratil,[6] and it seems

to be productive of symptoms and signs qualitatively, although not quantitatively, similar to the symptoms and signs observed in our patients. The quantitative dissimilarity might be explained on the basis of the size of dose employed for physiological research. Accordingly, it seems reasonable to infer that our patients had symptoms and signs by reason of hyperactivity of the parasympathetic system or hypoactivity of the sympathetic system, or, to express it in another fashion, a predominant orientation towards the parasympathetic side in autonomic activity.

The second question proposed above cannot receive a final answer in the light of our present knowledge. Symptoms and signs similar to these are not uncommon in those convalescing from acute illness such as typhoid fever, lobar pneumonia and in those with wasting diseases such as pulmonary tuberculosis or carcinoma. Fatigue, large meals and hot baths likewise seem to favor a parasympathetic orientation of autonomic activities. In a sense, one can demonstrate all these things by *a priori* experiment. To prove *a priori* that psychic factors can produce such symptoms and signs as observed in these patients is, however, quite impossible. Nevertheless, the effectiveness of psychotherapy in being followed by a disappearance of these symptoms and signs suggests that they were produced by psychic factors. Our series is too small to permit of generalization in this regard, but it does suggest that psychic factors can produce a predominantly parasympathetic orientation of the autonomic system.

The fact that Cannon has demonstrated by *a priori* experiment a sympathetic hyperactivity in an animal which is emotionally stimulated at once casts doubt upon our hypothesis as to an emotional origin for the phenomena which we observed. A moment's reflection makes clear an important difference between man and the lower animals. Both can, of course, rebel against an undesirable environmental situation, but the lower animal in Cannon's experiments rebelled against situations the menace of which might be overcome by the full utilization of his bodily resources, whereas man can, and oftentimes does, rebel not only against situations which can be overcome by his limited power but also against situations which he cannot overcome at all. Furthermore, man's rebellion against the inevitable and the unchangeable may be not the matter of a moment but the matter of days, of months, or of years. Analogous situations cannot be produced in a laboratory. It is, of course, true that one can observe in man the condition of hyperactivity of the sympathetic system, which is brought about by emotional factors, but in such cases the menacing influence is one which presumably can be overcome by the employment of all the bodily resources at man's disposal. These resources are mobilized through the activity of the sympathetic system. However, when man is faced by a menace which he cannot overcome (and menacing influences of this type confronted the patients discussed above), there

seems little utility in mobilizing the body's resources for such a contest. In such cases, hypoactivity of the sympathetic system, hyperactivity of the parasympathetic system, or a combination of both does not seem unreasonable to expect. In view of these considerations it is our belief, although our data is insufficient to prove this beyond reasonable doubt, that emotional situations brought about by a menace which is regarded as capable of being overcome is followed by predominantly sympathetic orientation of the autonomic system, but that emotional disturbances brought about by an insuperable menace are followed by predominantly parasympathetic orientation.

That these congeries of signs and symptoms have been observed only in the young does not seem particularly remarkable, when one considers that the mature oftentimes have irreversible changes in tissues as the concomitant of age. Irreversible changes would necessarily modify any symptom complex. Furthermore, a functional system complex, if prolonged, might be expected to result itself in irreversible anatomic change.

Summary. The symptoms, physical signs and laboratory data found in 20 patients, diagnosed as psychoneurotics, because of the absence of demonstrable physical disease and because of the effectiveness of psychotherapy in bringing about a cure, are reported as found before and after treatment. The symptoms, physical signs and laboratory data are similar to those which one would expect from stimulating the parasympathetic division of the autonomic nervous system.

The difficulties of employing the *a priori* scientific method in psychosomatic research are enumerated, in explanation of the fact that the conclusions in this paper are mostly obtained by *a posteriori* reasoning.

It is suggested that menacing influences which may be surmounted give rise to an emotion in which the predominant physical manifestations are due to stimulation of the sympathetic division of the autonomic nervous system; and that those which appear insurmountable give rise to an emotion in which the predominant physical manifestations are due to stimulation of the parasympathetic division of the autonomic nervous system.

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BOOK REVIEWS AND NOTICES.

ORAL HYGIENE AND THE TREATMENT OF PARODONTAL DISEASES. By RUSSELL W. BUNTING, D.D.Sc., Professor of Oral Histology and Pathology in the School of Dentistry of the University of Michigan, Ann Arbor. Pp. 187; 80 illustrations. Philadelphia: Lea & Febiger, 1936. Price, $2.50.

AFTER many years of experience, the author has presented this book for the use of students and practitioners of the dental profession in the sincere belief that mouth hygiene must be more thoroughly understood if the practice of dentistry is to fulfill its true purpose. The aim of this book is to indicate to practitioners in general that mouth health cannot be separated from general health.

The first section deals with oral hygiene proper and the salient features of oral sepsis, the prevention of dental caries, the prevention of parodontal infections and oral prophylaxis. The second section is devoted to an extensive discussion of parodontal diseases and their treatment. Gingivitis, parodontitis, pericemental abscess, Vincent's infection and gingival atrophy are presented in a comprehensive fashion. Facts are not merely presented but interpreted and explained.

The author has taken great care to select and review outstanding beliefs concerning the maladies discussed and to stress just those points which are interesting and important to know.

This is a book that might profitably be used by student, the practitioner and all those interested in Oral Hygiene and the relation of mouth sepsis to systemic diseases. T. C.

A TEXT-BOOK OF PATHOLOGY. By W. G. MACCALLUM, Professor of Pathology and Bacteriology, The Johns Hopkins University, Baltimore. Pp. 1277; 697 illustrations. Sixth Edition, entirely reset. Philadelphia: W. B. Saunders Company, 1936. Price, $10.00.

THE long continued and wide use of this text-book of pathology is an indication of its excellence. The new edition follows the previous system of arrangement of material on an etiological basis, rather than the arrangement usual in other text-books according to organs and systems. Two chapters on infections of uncertain nature, in the previous edition have been reclassified as a chapter on rickettsia infections and five chapters on filterable viruses. Rheumatism has been dealt with under the latter category because the author considers that "it seems probable that rheumatism is caused by one of those elusive filterable infective agents," although he gives no positive evidence to support this. This is a radical departure from the current concept of this disease. Equally surprising in his inclusion of scarlet fever as a virus disease, and of periarteritis nodosa as apparently a virus infection. This illustrates the difficulties of treating pathology on an etiological basis, and this system requires a discriminating reader. New chapters deal with fungus infections; with diseases of the central nervous system of unknown etiology; with teeth and related structures; and with congenital malformations. Injuries to organs of internal secretion now constitute six chapters instead of the former three. Many new illustrations from the author's own material are excellent, and as in previous editions, descriptions of pathological processes drawn from the author's personal experience are effective. I. Z.

AN INTRODUCTION TO MATERIA MEDICA AND PHARMACOLOGY. By HUGH ALISTER MCGUIGAN, PH.D., M.D., Professor of Materia Medica, Pharmacology, and Therapeutics, University of Illinois, College of Medicine, Chicago, and EDITH P. BRODIE, A.B., R.N., formerly Director School of Nursing, Vanderbilt University, Nashville; formerly Instructor in Materia Medica and Therapeutics, Washington University School of Nursing, St. Louis. Pp. 580; 71 illustrations and 18 color plates. St. Louis: The C. V. Mosby Company, 1936. Price, $2.75.

THE preface states that "this book is the outgrowth of an attempt to revise the Fourth Edition of Brodie's *Materia Medica for Nurses.*" The rising standards of the nursing profession are depicted in the scope and nature of this work. It contains a brief but well-done history of drug-giving. The chemical nature of drugs is shown by means of structural formulas; experiments illustrating various features in the action of drugs are described and numerous records are given. There is more direct correlation with bedside therapeutics and greater attention to the preparation and administration of drugs than is usual in books on pharmacology for medical students; controversial points are also treated briefly, and properly so in view of the purpose of the book. The only adverse criticism the reviewer can make against this work is that it may be too difficult for the average nurse. Certainly it affords an opportunity for acquainting student nurses with the facts of modern pharmacology and deserves serious consideration by those upon whom that task devolves. C. S.

DIGESTION AND HEALTH. By WALTER B. CANNON, George Higginson Professor of Physiology, Harvard Medical School. Pp. 160; 14 illustrations. New York: W. W. Norton & Co., Inc., 1936. Price, $2.00.

IN this small volume Dr. Cannon has described for the lay reader the nature of hunger and of thirst and has described the mechanism of autonomic control of gastro-intestinal function and the influence of emotion upon this control. In the exposition of his material Dr. Cannon has described in simple terms the classical experiments in these fields, including in certain instances graphs and figures from the original articles. He has thus allowed the lay reader to see the way in which scientific facts are accumulated. This method of presenting the subject-matter may be a little difficult for some readers to follow, but from the information so presented practical applications are indicated which should be understandable and of interest to the thoughtful layman. K. E.

THE CLINICAL USE OF DIGITALIS. By DREW LUTEN, A.B., M.D., Associate Professor of Clinical Medicine in the Washington University School of Medicine and Physician to Barnes Hospital, St. Louis. Pp. 226; 5 illustrations. Springfield, Ill.: Charles C Thomas, 1936. Price, $3.50.

A CONCISE, yet inclusive, discussion of digitalis therapy. The first portion of the book emphasizes important pharmacologic concepts. Then follow chapters on indications and contraindications; dosage and methods of administration; and the prognostic value of the response to digitalis. The final chapter, entitled Therapeutic Theses, is a group of summarizing aphorisms.

The author uses the historical approach effectively, to support the rationale of his arguments. The style is readable and emphatic. Some might criticise the omission of a rule-of-thumb outline for digitalis dosage. Most readers, however, will agree with the author's viewpoint when he refuses to do so. W. J.

A Dissertation on the Sensible and Irritable Parts of Animals. By Albrecht von Haller [London, J. Nourse, 1735]. Introduction by Owsei Temkin. Pp. 49; 1 illustration. Baltimore: The Johns Hopkins Press, 1936. Price, $1.00.

This reprint of an anonymous English translation of Haller's celebrated work is welcome both as an easily available form of an important physiological treatise and also, as Temkin points out in his introduction, as "an outstanding document of indefatigable experimentation and clear reasoning." Though the phenomena of sensibility and irritability (a term coined by Glisson) were recognized long before Haller, to him is due the credit for recognizing their independence and the clear distinctions between them. His line of reasoning is interesting to follow. E. K.

The Riddle of Woman. A Study in the Social Psychology of Sex. By Joseph Tenenbaum, M.D., Director of Urological Service in the Central Neurological Hospital, Welfare Island. Pp. 477. New York: Lee Furman, Inc., 1936. Price, $3.50.

In title, this book is designed for popular appeal and the approach to the subject-matter so definitely Freudian, that it will find but small favor with most physicians, Some of the angles from which Woman is discussed, are: A Social Problem, The Sex Urge in Woman, The Wife, The Bride, The Adultress, The Virgin, The Spinster, The Witch, The Beautiful Woman and The Prostitute. Freud is the author most frequently quoted together with "Albert Einstein, the greatest genius of the age." A vast amount of data are assembled and the "Riddle" is not solved. N. Y.

Chemical Procedures for Clinical Laboratories. By Marjorie R. Mattice, A.B., Sc.M., Assistant Professor of Clinical Pathology, New York Post-Graduate Medical School of Columbia University; Assistant Director of the Biochemical Laboratory, New York Post-Graduate Hospital; Consultant Chemist, Reconstruction Hospital, New York City. Pp. 520; 90 illustrations and 2 colored plates. Philadelphia: Lea & Febiger, 1936. Price, $6.50.

The author has organized a wealth of trustworthy procedures and valuable information into four groups:

Part I. Blood. Following a preliminary discussion of the functions and general properties of blood are given reliable procedures for determining the acid-base balance of the blood, carbohydrates and ketones, cholesterol and other lipids, plasma proteins, non-protein nitrogen and its components, hemoglobin, serum pigments and hepatic function tests, and inorganic constituents. The subject matter is extremely well organized and the tests are standard.

Part II. Clinical laboratory procedures of urine testing are presented in the same way as is the blood in Part I. It is quite thorough.

Part III. Gastro-intestinal Secretions. This is a trustworthy and gratifying section. The Lueder-Hollander System for estimating the duodenal enzymes is given.

Part IV. In this section is included both qualitative and quantitative methods of examination of miscellaneous biological fluids, such as milk, cerebrospinal fluid, and effusions.

Scattered through the text are practical discussions dealing with sources of error and methods of eliminating them. The interpretations are conservative yet thorough. This book is not to supplant standard texts of physiologic chemistry as its greatest use will be to clinical pathologists and their assistants. Every clinical laboratory should have a copy. J. B.

MEDICAL CLASSICS. Volume 1, No. 1 (September, 1936) (Ten issues a year). Compiled by EMERSON CROSBY KELLY, M.D., of the Department of Surgery, Albany Medical College. Pp. 78; illustrated. Baltimore: The Williams & Wilkins Company, 1936. Price, $10.00 per volume.

THE desirable vogue of reprinting important medical articles so that they are more easily available to the historically minded reader has further support in this new series of Medical Classics. In periodical form, more elastic and extensible than the books of this kind that have hitherto appeared, this venture need only be limited by the success of its reception. Let us hope that this will be conspicuous and that the series will have a long and useful career in stimulating the medico's interest in the historical side of his profession. This first number reproduces in their complete original form three of Paget's most important contributions. Who is there who will disagree with the compiler's view that "every doctor who has a patient with osteitis deformans or one in whom osteitis deformans is a possibility will be a better doctor if he knows intimately the writings of Paget on this subject?" And for that matter, even if he has not such a patient, will he not be a better doctor and one better satisfied with his profession, if he reads these brilliant descriptions and begins the habit, if he has not already formed it, of going back to the masters' original descriptions? Not the least useful in this number, is a bibliography of 175 medical articles by Paget. We should welcome most heartily this latest addition to the armamentarium that brings the high spots of medical history the more easily to our aid. E. K.

OPERATIVE AND INTERPRETIVE RADIODONTIA. A Textbook for Students and Practitioners of Dentistry. By WALTER S. THOMPSON, D.D.S., Associate Professor of Radiodontia, College of Dentistry, University of Southern California; Lieutenant, U. S. N. R., Special Service Instructor in Radiodontia, etc. Pp. 374; 355 illustrations. Philadelphia: Lea & Febiger, 1936. Price, $7.00.

THIS volume is a concise and comprehensive presentation of roentgenology as applied to dentistry, written in an attractive and readable style. The first part deals with operative radiodontia in which there is introduced the history of radiodontia, followed by the physics of Roentgen rays, with a consideration of the mechanical appliances employed in radiodontia, the technique of dental roentgenology and the processing of dental films. Particularly commendable is the chapter devoted to the biological effects of Roentgen rays, in which special emphasis is placed on the danger inherent in their use. Important is the consideration given to the roentgenological aspects of the structures in the proximity of the dental arches, such as the maxillary sinuses and the salivary glands. The technique for the use of diagnostic-radiopaques is included. Many special procedures to be used in the occasional case are described. The text is amply and beautifully illustrated.

Interpretative radiodontia is dealt with in considerable detail. This is introduced by a consideration of Roentgen ray absorption and followed by interpretative studies based on dental anatomy and pathology. The closing chapter on radiation therapy indicates that this work is quite modern in every respect. The author rightfully infers that radiation therapy is a fruitful field for future researches in dentistry.

This volume will have a wide appeal, not alone for students and practitioners of dentistry, for whom it will serve as an excellent text and reference work, but also for the general roentgenologist, who is required to possess considerable knowledge of radiodontia. K. K.

DIE NEBENNIERENRINDE. Beiträge zur Experimentellen und Klinischen Pathologie. By DR. MED. SIGISMUND THADDEA, Assistent der II. Med. Universitätsklinik der Charité, Berlin. Pp. 199; 78 illustrations and 36 tables. Leipzig: Georg Thieme, 1936. Price: Paper, M. 11.; Bound, M. 13.

THIS book is essentially a rather extensive review of the literature and the author's own experiments concerning the adrenal cortex. Emphasis is placed upon the metabolic and physiologic aspects. Historical and morphological considerations and details as to preparations of active extracts are but briefly discussed.

The main sections deal with muscle weakness, growth, temperature, water, mineral, blood, circulation and respiratory changes, and most thoroughly with metabolism. Especially interesting are the author's experiments concerning carbohydrate and cholesterol metabolism. Unfortunately his experiments are not given in detail; many simply confirm previous work. In the majority of experiments reported no mention is made as to whether or not salt was used.

The last portion is devoted to Addison's disease, adrenal cortical hormone therapy and relationship of the adrenal cortex to the other endocrine glands and to the vitamins. The book is succinct and well organized, having numerous subheadings. There are no descriptions of technique. It may be recommended to those interested in endocrine or metabolic problems.

C. D.

LANE MEDICAL LECTURES: STUDIES IN CARDIOVASCULAR REGULATION. By G. V. ANREP, M.D., D. Sc., F.R.S., Professor of Physiology, Medical Faculty, Egyptian University, Cairo, Egypt. Pp. 118; 38 figures and 8 tables. Stanford University, Calif.: Stanford University Press, 1936. Price: Paper, $1.50; Cloth, $2.25.

THE five lectures contained in this book deal with 1, The Proprioceptive Mechanism of Cardiovascular Regulation; 2, The Respiratory Regulation of the Heart Rate; 3, The Dynamics of the Coronary Circulation; 4, The Coronary Blood Flow and 5, The Blood Flow Through Skeletal and Plain Muscles.

The author, in addition to being a distinguished investigator in the field of circulatory physiology, proves himself to be an excellent interpreter of the highly technical literature of the subject. The lectures are couched in simple language and the thought is easy to follow. This little volume is highly recommended to all who wish to keep track of what the physiologists are accomplishing by their researches on the circulation.

C. W.

A PRACTICAL MEDICAL DICTIONARY. By THOMAS LATHROP STEDMAN, A.M., M.D. Pp. 1282; illustrated. Thirteenth Edition, revised with the New British Anatomical Nomenclature (9 pages). Baltimore: William Wood & Co., 1936. Price, $7.50 with thumb index; $7.00 without.

ALWAYS one of our best medical dictionaries, with the advantage of 25 years under the same editor, this work appears in a new edition that has included hundreds of new terms and various changes that put it in accord with the 1936 U. S. Pharmacopœia. Especially interesting to the Reviewer are the initial pages from the Eleventh Edition Preface and on Medical Etymology, wherein are given rules and examples of proper spelling and the history of the editor's successful struggle to extinguish errors (such as improper omission of the final e, change of k for c, etc.) that had been promoted in other quarters.

E. K.

PSYCHIATRY FOR PRACTITIONERS. [Reprinted from Oxford Loose-Leaf Medicine.] By various authors. Edited by HENRY A. CHRISTIAN, A.M., M.D., LL.D., Sc.D. (HON.); Hersey Professor of the Theory and Practice of Physics, Harvard University; Physician-in-Chief to the Peter Bent Brigham Hospital, Boston. Pp. 646. New York: Oxford University Press, 1936. Price, $6.50.

THIS reprint from Oxford Loose-Leaf Medicine is by 11 collaborators. E. A. Strecker and H. D. Palmer contribute the recognition and management of the beginning of mental disease; Gerald Pearson, psychiatry of childhood; Earl D. Bond, post-encephalitic and post-traumatic behavior disorders; E. A. Whitney, mental deficiency; Eugen Kahn, psychopathic personalities; F. G. Ebaugh, toxic reaction types; W. A. White, paranoia and paranoid conditions; C. O. Cheney, dementia præcox (schizophrenia) group; D. K. Henderson, affective reaction type (manic-depressive) including involutional melancholia; T. A. Ross, psychoneuroses.

Toxic reaction types is an excellent chapter and since the induction of malaria in the treatment of paresis is so admirably considered, it need not have been described elsewhere. Chapters on affective reaction types and psychoneuroses are worthy of special mention. Too many historic characters are classed as epilepties, *e. g.*, Byron, Peter the Great and Napoleon. Once when Kean was acting, many in the audience were overcome and Byron fell into a fit which appeared to be hysterical; his feet were deformed but not from a central lesion—they were club-feet. As to Peter the Great and Napoleon, each was a *tiqueur;* the latter, after long hours of work would at times show a tic—frequent and rapid elevation of the right shoulder—which to those unfamiliar, was sometimes mistaken for a gesture of disapproval. The terms "Post-traumatic neuroses" and "psychoses" should be written with the "post." The book serves its purpose well, but it is hoped a subsequent edition will contain a more complete index. A glossary would aid general practitioners greatly. N. Y.

A TEXTBOOK OF SURGERY. By JOHN HOMANS, M.D., Clinical Professor of Surgery. Compiled from Lectures and Other Writings of 23 Members of the Surgical Department of The Harvard Medical School. With a Special Bibliographical Index and illustrations by Willard C. Shepard. Pp. 1267; 530 illustrations, Fourth Edition. Springfield, Ill.: Charles C Thomas, 1936. Price, $8.00.

THE appearance of this work so quickly in its Fourth Edition demonstrates that it has met the needs of the professional public in this particular branch—surgery. The book is an extremely popular one for students, practitioners and specialists alike. It covers the field completely and sufficiently thoroughly to satisfy the needs of its readers. This edition has been entirely re-written as well as re-edited; all old material has been replaced with new and there has been added a chapter on Amputations and Plastics. Revision has taken into consideration such subjects as Antiseptics and Sterilization, the Sympathetic Nervous System and the Thyroid Gland. Much valuable information has been added with regard to certain fractures, yet, with all of these additions the size of the volume has not been materially changed.

Recognizing the fact that it is an extremely difficult problem to write a one volume surgery to meet all needs, the Reviewer thinks that this particular work fulfills the aim as near as possible under the present conditions.

The subject matter is covered in a sufficiently comprehensive manner to fit practically all requirements. The book is all that is necessary for the student and at the same time has sufficient reference value to be a handy work for the specialist. E. E.

PRINCIPLES OF BIOCHEMISTRY. By ALBERT P. MATHEWS, Carnegie Professor of Biochemistry, University of Cincinnati, Cincinnati, Ohio. Pp. 512; 3 illustrations. Baltimore: William Wood & Co., 1936. Price, $4.50.

THIS book is presented as a completely new and rewritten textbook for students of medicine and is not to be regarded in any sense as a revision of Dr. Mathews' older and formerly widely used textbook on Physiological Chemistry.

In his preface the author sets up as one aim the presentation of the subject in such way that it "will appear, not as an inchoate assembly of facts, but as making part of a great science which reveals the finer structure and coördinated chemistry of the human body." In this laudable attempt, Dr. Mathews has not, in the opinion of this Reviewer, been uniformly successful. One often feels, in reading the book, that unfortunately little discrimination has been used between topics of prime physiological importance and others that hardly merits any space whatever. This produces an effect of giving a large mass of uncorrelated information, important and unimportant, with very little critique to guide the student.

For example, the general topic of acid-base balance as reflected in both blood and urine is given very scanty attention; and on page 373, in discussing acid-base balance two paragraphs of equal length deal, respectively, with the effects of various foods on the alkalinity of the urine and with the effect of cancer and other conditions on the pH of blood. It would seem that the effect of various foods on acid-base balance would far outweigh, in importance, a topic so controversial and so little substantiated as the effect of cancer on blood pH. Other examples of such unbalanced treatment could be mentioned.

Part V, dealing with the vitamins and hormones appears to be a very valuable part of the book. The author's treatment of these topics is full and as nearly up-to-date as could be expected in so active a field.

The book is compact, well arranged and is written for the most part in Dr. Mathews characteristically interesting style. J. A.

THE GIFT OF COLUMBUS. By CHARLES C. DENNIE, M.D., Kansas City, Mo. Pp. 195. Kansas City, Mo.: Brown-White Co., 1936. Price, $2.00.

THIS book has been prepared for those who have not yet acquired syphilis, but who may do so. In general, it takes a sound attitude toward the proper ways of sociologically combating the spread of the disease and of medically treating those unfortunate enough to have acquired it. It is particularly appropriate at this time, when Surgeon General Parran is so efficiently bringing the fight against "the social disease"—a euphemism used more than once even in this book—out into the open. All the more disappointing is it then, to be unavoidably struck by the book's shortcomings. The title has novelty, to be sure, as the author uses it to mean that Columbus' crew brought syphilis to the West Indian natives! But why ignore the mass of evidence to show that syphilis existed in the Western World before Columbus? Typographical errors ("agrecake," "high domed literatuers," etc.) vie with questionable or incorrect statements ("95% of those so afflicted [aortic regurgitation and aortitis] have to thank syphilis"); while the company of mis-spelled worthies is indeed a motley one (for instance, "Lazarius Reverius, Oveido, Fornier, Montego, Wasserman, Erlich, Loewenhoeck, Jonothan Hutchinson, Colle"). Even a book for popular consumption, deserves greater accuracy than this. E. K.

BRITISH MASTERS OF MEDICINE. Edited by SIR D'ARCY POWER, K.B.E., F.R.C.S., F.S.A., Consulting Surgeon and Archivist to St. Bartholomew's Hospital; Honorary Librarian, Royal College of Surgeons of England. Pp. 242; illustrated. Baltimore: William Wood & Co., 1936. Price, $3.00.

INTERMEDIATE in size between the short notes of a biographical dictionary and the monographs that are necessarily restricted to the more famous, these 24 articles give us a pleasant picture of British medicine from Harvey to Starling, together with sympathetic personal sketches, each with portrait, "written by those who have been attached to the great institutions which their heroes made famous." While obviously accounts of Sydenham, Hunter, Lister and others of that ilk can easily be found elsewhere, a new interpretation may always be interesting; and for such as Floyer, Willan, William Ferguson, R. B. Todd, one might have to make a considerable search for an equally satisfying presentation. The moderns included are William Turner, Owen Thomas, Robert Jones, Manson, Osler, Mackenzie, Starling. The articles are reprinted from the pages of the *Medical Press and Circular;* the initials of the author of each sketch are found in a list following the List of Illustrations. E. K.

ATLAS OF CONGENITAL CARDIAC DISEASE. By MAUDE E. ABBOTT, B.A., M.D., F.R.C.P. (CANADA), Curator of the Historical Medical Museum and Assistant Professor of Medical Research, McGill University, Montreal, Canada. Foreword by DR. PAUL D. WHITE. Pp. 72; 25 plates with more than 200 illustrations. New York: American Heart Association, 1936. Price, $5.50.

MAUDE ABBOTT writes with recognized authority on the subject of Congenital Heart Disease, and anything that emanates from her pen needs no laudatory introduction nor recommendation. Her new Atlas of Congenital Cardiac Disease, however, is particularly worthy of praise. For those readers who feel they have neither the special interest nor the time to read her monographs, this all-too-short atlas uniquely fills a gap in essential clinical knowledge.

Part I deals with the development and comparative anatomy of the heart. Part II presents the clinical classification of Congenital Cardiac Disease. The atlas is replete with case presentations and clinical features, diagrams, illustrations of specimens, roentgenograms, electrocardiograms and a full bibliography. A valuable addition is the statistical table of 1000 analyzed cases. This excellent atlas serves to whet an already impatient appetite for the larger volume on Congenital Cardiac Disease which the author is preparing. A. M.

RECENT ADVANCES IN ALLERGY. (Asthma, Hay-Fever, Eczema, Migraine, etc.). By GEORGE W. BRAY, M.B., CH.M. (SYDNEY), M.R.C.P. (LONDON), Physician in Charge of Children's Department, Prince of Wales Hospital; Assistant Physician, Princess Elizabeth of York Hospital for Children, etc. With Foreword by ARTHUR F. HURST, M.A., M.D. (OXON.), F.R.C.P., Senior Physician, Guy's Hospital, etc. Pp. 517; 107 illustrations, including 4 colored plates. Third Edition. Philadelphia: P. Blakiston's Son & Co., Inc., 1937. Price, $5.00.

WITH 13 additional pages of text and some 2000 references to the literature, the new edition of this excellent work is highly recommended to students and practitioners as a well-rounded treatise on allergy. Its only disadvantage from the American standpoint continues to be the lack of hay fever plant surveys for this country. R. K.

ATLAS OF HUMAN ANATOMY, with Explanatory Text. By JESSE FEIRING WILLIAMS, M.D., Columbia University. Colored illustrations by Franz Frohse, University of Berlin, and Max Brödel and Leon Schlossberg, of Johns Hopkins University. Pp. 64. New York: Barnes & Noble, Inc., 1935. Price, Paper, $1.25; Cloth, $2.00.

THIS book, "designed for both the layman and the student of anatomy," contains a surprisingly large amount of information in a small space. Also the names of the illustrators are sufficient guarantee for the accuracy of the beautiful drawings. Yet with its brief text it is far from a substitute for a standard textbook for the medical student—probably was not so intended—and should only serve the medical man in such ways as when he wishes to demonstrate to his patient. E. K.

TREATMENT IN PSYCHIATRY. By OSKAR DIETHELM, M.D., Professor of Psychiatry, Cornell University Medical College, New York; Psychiatrist-in-Chief, the New York Hospital (Payne Whitney Psychiatric Clinic), etc. Pp. 476. New York: The Macmillan Company, 1936. Price, $4.00.

MUCH reverence is shown herein to the author's former master, Adolf Meyer, whose psychobiology, "the hypothesis that matter and its functions belong inseparably together, forming a unit . . . and known as the principle of integration," threads its way through the book. Important chapters are: study of personality; suggestion and hypnosis; psychoanalytic procedure; excitements; depressions; schizophrenic reactions; paranoid and paranoiac reactions; psychoneuroses; stuttering, tics, occupational reactions and psychopathic personalities.

Psychoanalysis as expounded by Freud, Adler, Jung and others, is given; and Kronfeld's "psychagogy," scientific re-education that does not tend to be exclusively individualistic, is described. It is stated Meyer coined the term, "mental hygiene," but Sweetser, in 1850, wrote a volume bearing the title. The book under review, with 45 case reports, contains new and useful information, but a more systematic arrangement would add to its usefulness. The chapter on depressions consists of 32 pages with no subdivisions, and in the index nothing pertinent follows depressions that would direct attention to any of its details. N. Y.

ON THE DISTURBANCE OF THE CIRCULATION IN SPINAL ANESTHESIA. An Experimental Study. By OSCAR O. SCHUBERTH. Pp. 77; 2 illustrations and 30 tables. Stockholm: P. A. Norstedt & Sons, 1936. (Price not given.)

THIS little monograph records the data and conclusions of Schuberth after an exhaustive study of the dynamic disturbances of the circulation in experimental spinal anesthesia. In the major portion of the work the experimental investigations were done on animals but limited observations were made on man. There is an introduction and two major subdivisions. The one, "The influence of spinal anesthesia on certain circulatory factors," considers oxygen consumption, arteriovenous oxygen difference, cardiac output, venous pressure, the blood volume and the capillary picture. The second deals with the influence on respiration of spinal anesthesia, involving the dorsal, but not the cervical cord. Each section consists of a short survey of previous investigations and these are followed by the author's data and discussion. The author concludes that the shocklike state which may accompany spinal anesthesia is different from most other types of shock in that there is no decrease in the circulating blood volume. This monograph is the best that the Reviewer has seen on the subject. There is a summary and an excellent bibliography. I. R.

DISEASES OF THE CORONARY ARTERIES AND CARDIAC PAIN. Edited by ROBERT L. LEVY, M.D., Professor of Clinical Medicine, College of Physicians and Surgeons, Columbia University; Associate Visiting Physician and Cardiologist, Presbyterian Hospital, New York City. Advisory Editorial Committee: ALFRED E. COHN, JAMES B. HERRICK, CARL J. WIGGERS; 14 Contributors. Pp. 445; 97 illustrations. New York: The Macmillan Company, 1936. Price, $6.00.

FEW branches of medicine have made more progress in this century than has the knowledge of cardiovascular disease, and no branch of cardiovascular study has progressed more in the past 20 years than has the study of the coronary arteries. Establishment of the criteria for recognizing coronary occlusion by James Herrick—one of the contributors to this volume—not only was of prime importance on its own account but apparently initiated fruitful studies in the anatomy, physiology and pathology of this vital part of the arterial tree. These studies have formed the core about which 14 of the leading students of the coronaries in this country have collected 17 chapters on the nature of coronary disease, its recognition and frequency and its medical and surgical treatment. Physicians, surgeons and their preclinical colleagues all should find this a timely, interesting and valuable—for many, invaluable—book. E. K.

LECTURES ON EMBOLISM AND OTHER SURGICAL SUBJECTS. (The Abraham Flexner Lectures, Series No. 4.) By GUNNAR NYSTROM, M.D., Professor of Surgery, University of Uppsala, Sweden; Chief of the Surgical Clinic and Director of the University Hospital, Uppsala. Pp. 213; 22 illustrations. Baltimore: Williams & Wilkins Company, 1936. Price, $3.00.

THIS interesting little volume contains 5 chapters representing 5 formal lectures given by Professor Nystrom at Vanderbilt University. The first is on "Embolism of the Arteries of the Extremities and Its Treatment;" the second on "Pulmonary Embolism and Its Surgical Treatment;" the third, "Swedish Experiences in Combating Appendicitis;" the fourth, "The Cytology of Joint Exudates as an Aid to Diagnosis;" the fifth, "The Treatment of Medical Fractures of the Collum Femoris."

The chapters on embolism are fascinating and all full of advice on diagnosis and treatment. In this field the Scandinavian surgeons have played the most important rôle. In the lecture on appendicitis the treatment of this common surgical lesion serves to portray the general nature of the practice of surgery in Sweden. The lecture on the cytology of joint exudates adds an interesting chapter to our knowledge of the cytology of effusions of the pleura and peritoneum. In the chapter on fractures of the neck of the femur the author pays high tribute to the work of American surgeons in this field. The lectures are simply but well illustrated and considerable statistical data are included in numerous tables. The volume forms a welcome addition to the surgical essays which have recently been published in this country. I. R.

THE PHYSIOLOGY AND PHARMACOLOGY OF THE PITUITARY BODY. By H. B. VAN DYKE, Professor of Pharmacology, Peiping Union Medical College, Peiping, China. Pp. 577; 55 illustrations. Chicago: The University of Chicago Press, 1936. Price, $4.50.

THIS is an excellent review of the voluminous literature on the pituitary. The bibliography alone covers 181 pages. The data described are well systematized, so that one can look up desired points with ease. The 55 illustrations are exceedingly well selected. We believe that this will be a valuable aid to students and investigators in this field. I. Z.

THE PRINCIPLES OF BACTERIOLOGY AND IMMUNITY. By W. W. C. TOPLEY, M.A., M.D., M.Sc., F.R.C.P., F.R.S., Professor of Bacteriology and Immunology, University of London; Director of the Division of Bacteriology and Immunology, London School of Hygiene and Tropical Medicine, and G. S. WILSON, M.D., F.R.C.P., D.P.H., Professor of Bacteriology and Applied Hygiene, University of London, London School of Hygiene and Tropical Medicine. Pp. 1645; 276 illustrations and 192 tables. Second Edition. Baltimore: William Wood & Co., 1936. Price, $12.00.

IT is not surprising that such an actively progressive subject as bacteriology should require new presentations at frequent intervals. This book, acclaimed as a leader shortly after its first appearance in 1929, retains its premier position in its new form. Admittedly more comprehensive than the average textbook for medical students, it has been found in at least one of our medical schools to be the most desirable to put in the student's hands, with recommendations for selective topical reading. Thus properly used, the wealth of detail constitutes an asset for a reference book, without harming its value as a students text. The extensive alterations that new concepts and facts have required have not changed the original plan or arrangement nor greatly increased the book's size. E. K.

THE LUNG. By WILLIAM SNOW MILLER, Emeritus Professor of Anatomy, University of Wisconsin. Pp. 209; 152 illustrations, including 20 colored plates. Springfield, Ill.: Charles C Thomas, 1937. Price, $7.50.

THIS is a monograph on the structure—especially the microscopic structure—of the lung. Its greatest value lies in its superb illustrations, because these enable the reader to grasp and understand pulmonary structure in three dimensions. The two dimensional pictures familiar to the microscopist is a very different thing, and scarcely gives an inkling of the relations of respiratory bronchioles, atria, air sacs and alveoli as reconstructed by Dr. Miller from serial sections. Besides the section on the anatomy of the air passages, there are chapters on blood vessels—the richness of the capillary network is astonishing—the lymph nodes, lymphoid tissue, nerves and pleura. A remarkable feature is a well-illustrated chapter on the structure of the lung as conceived by other anatomists from Malpighi to the present time.

With Dr. Miller's conclusions on such controversial subjects as the epithelial lining of the alveoli and the presence or absence of alveolar pores, the reader may or may not agree. But all sides of these questions are covered by citations from the literature, and the author's own position is supported by good photomicrographs.

In conclusion, the Reviewer wishes to commend a notably fine example of book making. M. McC.

BAILEY'S TEXT-BOOK OF HISTOLOGY. (Elwyn and Strong.) By PHILIP E. SMITH, Professor of Anatomy, Editor, RUSSELL L. CARPENTER, PH.D., WILFRED M. COPENHAVER, PH.D., CHARLES M. GOSS, M.D., AURA E. SEVERINGHAUS, PH.D., all Assistant Professors of Anatomy, College of Physicians and Surgeons, Columbia University. Pp. 773; 506 illustrations, some in colors. Ninth Edition, revised and rewritten. Baltimore: William Wood & Co., 1936. Price, $6.00.

IN this edition all chapters but one have been changed and four have been rewritten—so great is the progress in even such a static subject as normal histology. The work continues to be primarily for medical students though "major controversial differences of opinion" have been included. The editors continue to emphasize that "structure assumes its full meaning only when correlated with function." E. K.

THE DEVELOPMENT OF MODERN MEDICINE. An Interpretation of the Social and Scientific Factors Involved. By RICHARD HARRISON SHRYOCK, Professor of History, Duke University. Pp. 442; illustrated. Philadelphia: University of Pennsylvania Press; London: Oxford University Press, 1936. Price, $4.00.

MEDICAL historians have become increasingly aware of the need of considering their field as but a branch of the history of science, and this, in turn, of the history of the world. The story is necessarily fragmentary if these backgrounds are not given their due position. Conversely, the general historian should find the art and science of medicine a desirable field of study, and yet how seldom does he invade it and how often is medical history written by those untrained historically! This attempt, then, by a professional historian "to portray certain major aspects of medical development against the background of intellectual and social history in general" has an added value in closing a long open gap. Those physicians who are at all historically minded will not be surprised at the general conclusion drawn; namely, that measurement, experiment and the use of instruments have been chiefly responsible for the advance of medical science; yet he probably will be surprised, and certainly should have his curiosity aroused, by the emphasis laid on such discussions as the failure of physical science in the 18th century, the social factors concerned in the medical lag, the loss of the public's confidence in the early 19th century, and its reacquisition at the end of the same century.

In this book the reader will find little about the outstanding men of our profession and nothing about the medicine of antiquity or of barbarous countries; but he will find an accurate, logical consideration of modern medical developments, traced from an unusual point of view, which should give him a better background for 20th century problems of medicine than does the conventional history of medicine. E. K.

SKIN DISEASES IN CHILDREN. By GEORGE M. MACKEE, M.D., Professor of Clinical Dermatology and Syphilology, New York Post-Graduate Medical School, Columbia University, and ANTHONY C. CIPALLARO, M.D., Associate in Dermatology and Syphilology, New York Post-Graduate Medical School, Columbia University. Pp. 344; 153 illustrations. New York: Paul B. Hoeber, Inc., 1936. Price, $5.50.

THERE is nothing to criticize adversely in this book. It is splendidly bound, printed on heavy enamel stock and in large clear type. The 153 illustrations are without exception models of art, clarity and critical selection. Needless to say, the entire field is covered. The literary style is crisp and the thoughts are therefore easily followed. The subject matter is down to date. The sections on treatment will appeal particularly to the practitioner; they are ample and yet not verbose. In short this book will remain for years as a model for bringing the dermatology of children to the pediatrist, concisely, adequately and pleasantly. F. W.

INTERNATIONAL CLINICS. Vol. IV. Forty-sixth Series, 1936. Edited by LOUIS HAMMAN, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, Md., with 14 Collaborators. Pp. 351; many illustrations and one colored plate. Philadelphia: J. B. Lippincott Company, 1936.

MOST striking in this issue are the colored illustrations of gastric lesions as seen by the gastroscope. Even with allowance for considerable diagrammatization, the potentialities of this method are shown obviously to be far from exhausted. "Xerostemia" in the Table of Contents proved disappointing when the text was found to add but little to the subject, xerostomia. Except for two progress articles on dermatology, the topics are all medical. E. K.

COSMETIC DERMATOLOGY. With dictionary of ingredients; discussion of anatomic physiologic, and pharmacologic bases of cosmetic application; "shelf-tested" formulary; and appendices on odor and color in cosmetics. By HERMAN GOODMAN, B.S., M.D. Pp. 591. New York: McGraw-Hill Book Co., Inc., 1936. (No price given.)

IT is clear that this book was designed primarily for the "dermatologist" of the beauty parlor. The dermatologic physician is only incidental; for example, there are sections on "head and body lice," "clothes lice" and "pubic lice." In many places the literary style drops to that of colloquialism such as "sales of clay go drooping with stock market averages." Nevertheless this is a unique work in a department of dermatology which is a definite part of medical dermatologic practice. Methods in cosmotology are not uniform among American dermatologists, and nothing has been seriously undertaken thus far to collect the data, analyze and record them. Doctor Goodman has done this. He has now supplied a place where dermatologists may check their position and a given point of departure for future condensation and supplementation of data of this sort.

About one-third of the book is really a pharmacopeia adapted to needs in cosmetology. Thereafter, the treatment of specific conditions is taken up as indicated by the following headings:—acne and facial blemishes, baldness, bleaching, cleansing creams and lotions, depilatories, face powders and rouge, hair dyeing, lip and nail preparations, shaving accessories and sunburn. Any author is on treacherous ground when writing in a border line field between legitimate medicine and such lay fields as cosmetology, physical therapy, and so on—particularly at the present day when so many non-medical "experts" are conducting a guerrilla invasion beyond their own province. Acne vulgaris and "facial blemishes" (melanotic moles!) are in point, involving as they do problems in differential diagnosis which may concern important general constitutional states like tuberculosis and cancer. It is trusted that this serious danger will be taken care of in Dr. Goodman's book. In any event, the volume is a miniature encyclopedia which stands alone in its field and to which the dermatologist will be constrained to turn frequently. F. W.

NEW BOOKS.

The Fundamentals of Electrocardiographic Interpretation. By J. BAILEY CARTER, M.D., Clinical Instructor, Department of Medicine, Rush Medical College, The University of Chicago; Associate Staff, Cook County and Augustanna Hospitals, Chicago. With a Foreword by HORATIO BURT WILLIAMS, M.D., Dalton Professor of Physiology, College of Physicians and Surgeons, Columbia University, New York. Pp. 326; 250 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price, $4.50.

Sickness and Insurance. A Study of the Sickness Problem and Health Insurance. By HARRY ALVIN MILLIS, Professor of Economics, The University of Chicago. Pp. 166. Chicago: The University of Chicago Press, 1937. Price, $2.00.

The Kinesiology of Corrective Exercise. By GERTRUDE HAWLEY, M.A., Assistant Director, Women's Gymnasium, Stanford University, California. Pp. 268; 107 illustrations. Philadelphia: Lea & Febiger, 1937. Price, $2.75.

The Medical Clinics of North America. Vol. 21, No. 1 (Chicago Number—January, 1937). Pp. 330; illustrated. Philadelphia: W. B. Saunders Company, 1937.

St. Thomas's Hospital Reports, Second Series, Vol. 1. Editors: Professor O. L. V. S. De Wesselow, Mr. C. Max Page, assisted by Mr. N. R. Barrett, Dr. J. St. C. Elkington, Dr. A. J. Wrigley. Pp. 199; illustrated (3 in color). London: St. Thomas's Hospital, 1936. Price, 7s. 6d.

Maternity and Post-Operative Exercises (Twenty-one Exercises). In Diagrams and Words by Margaret Morris, C.S.M.M.G., in collaboration with M. Randell, S.R.N., S.C.M., T.M.M.G. Introduction to Maternity Exercises by Professor R. W. Johnstone, C.B.E., M.D., F.R.C.S.E., F.C.O.G., Introduction to Post-Operative Exercises by Professor John Fraser, M.C., M.D., F.R.C.S.E. Pp. 152; illustrated. New York: Oxford University Press, 1936. Price, $2.00.

Reading, Writing and Speech Problems in Children. A Presentation of Certain Types of Disorders in the Development of the Language Faculty. By Samuel Torrey Orton, M.D., Former Professor of Neurology and Neuropathology, Columbia University. Pp. 215; 24 illustrations. New York: W. W. Norton & Co., Inc., 1937. Price, $2.00.

The Prophylaxis and Treatment of Rheumatic Disease Through Photofixation of Pathogenic Antigens. By S. Peskind, B.S., M.D., Cleveland, Ohio. Pp. 12. Cleveland: The S. P. Mount Printing Company, 1936.

An Introduction to Medical Science. By William Boyd, M.D., M.R.C.P. (Edin.), F.R.C.P. (Lond.), Dipl. Psych., F.R.S. (Canada), Professor of Pathology in the University of Manitoba; Pathologist to the Winnipeg General Hospital, Winnipeg, Canada. Pp. 307; 108 illustrations. Philadelphia: Lea & Febiger, 1937. Price, $3.50.

Papworth Research Bulletin, Vol. 1, No. 1. The Sims-Woodhead Memorial Laboratory. Pp. 59; illustrated. Papworth: At the Papworth Press, 1936.

This contains 9 articles and 4 lists of papers published by members of the staff. As the articles have scientific value it is regrettable that they are not given a medium of wider circulation.

Endocrinology. Clinical Application and Treatment. By August A. Werner, M.D., F.A.C.P., Assistant Professor of Internal Medicine, St. Louis University School of Medicine; Associate Physician, St. Mary's Group of Hospitals, etc. Pp. 672; 265 illustrations. Philadelphia: Lea & Febiger, 1937. Price, $8.50.

Clinical Roentgenology of the Cardio-vascular System. Anatomy, Physiology, Pathology, Experiments and Clinical Applications. By Hugo Roesler, M.D., Associate Professor of Roentgenology and Cardiologist, Department of Medicine, Temple University School of Medicine; Cardiologist, Temple University Hospital, etc. Pp. 343; 199 illustrations. Springfield, Ill.: Charles C Thomas, 1937. Price, $7.50.

International Clinics, Vol. 1, Forty-Seventh Series, 1937. Edited by Louis Hamman, M.D., Visiting Physician, Johns Hopkins Hospital, Baltimore, Md., with 14 collaborators. Pp. 310; illustrated (1 colored plate). Philadelphia: J. B. Lippincott Company, 1937.

The 19 articles of this volume deal chiefly with cardio-renal system, the lungs and the thyroid. The progress article is on carbohydrate metabolism. The execution of the colored frontispiece reminds one of the atlases of a century ago.

Vascular Disorders of the Limbs. Described for Practitioners and Students. By Sir Thomas Lewis, C.B.E., F.R.S., M.D., D.Sc., LL.D., F.R.C.P., Physician in Charge of Department of Clinical Research, University College Hospital, London; Consulting Physician, City of London Hospital, etc. Pp. 111, 5 illustrations. New York: The Macmillan Company, 1936. Price, $2.00.

PROGRESS
OF
MEDICAL SCIENCE

GYNECOLOGY AND OBSTETRICS

UNDER THE CHARGE OF
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TUBAL DISEASES AND PELVIC INFLAMMATIONS.

Of all the diseases which may affect the Fallopian tubes, inflammations are the most common and in this group the gonococcus is the most frequent causative agent. It is too often assumed, however, that the gonococcus is exclusively responsible for tubal and pelvic infections; other organisms are frequently of great etiologic importance affecting not only the diagnostic signs but also the choice of treatment. This subject has been well presented by Aldridge[1] based on his experience at the Woman's Hospital in New York. He states that 70 to 75% of all cases of salpingitis are gonorrheal in origin, but by the time the patients come under observation, the cause cannot be determined in a high percentage of cases. The disease is a self limited one which tends to heal spontaneously by autosterilization and in about 85% of cases healing would be complete provided reinfection could be prevented. Infections other than specific ones, are caused by organisms which may continue to live in the tissues for indefinite periods of time, regardless of symptoms but they also tend to heal spontaneously. Nature's success in healing such inflammations depends upon the type of infection and the period of time allowed for healing to take place. Death from general peritonitis caused by extension of infection from the tubes or their rupture is extremely rare. Accepting the foregoing facts, it is obvious that any attack of such inflammation should first be treated by palliative means and most gynecologists are becoming more conservative as time goes on. The result has been a great increase in the number of spontaneous cures, proving that many operations previously done were unnecessary. In Aldridge's experience protein therapy has proved very efficacious and has often kept patients sufficiently symptom-free to enable them to continue with their routine duties while healing was going on. In general, palliative hospital treatment consisted of rest in

bed until the patients were afebrile and subjective symptoms had practically disappeared. During this time the inflammatory exudate usually became absorbed. About half of the attacks were treated by protein injections using sterilized cow's milk. Sedatives and hot or cold applications to the abdomen were used as necessary to relieve pain. Warm vaginal douches were given routinely, not only relieving pain but assisting in the absorption of the exudate. An effort should be made to eliminate infections of the external genitalia from which recurrent infections might occur. If collections of pus bulge in the vaginal vault, they should be opened by posterior colpotomy. Operation may be required in the chronic stage of the disease for recurrent attacks of pain and disability but not merely because palpable adnexal masses are present. In his series of 1021 attacks treated by palliative methods, approximately one-half (48%) either healed completely or became free from symptoms so that operation was not necessary; $\frac{1}{3}$ persisted after treatment with symptoms and palpable masses some of which had to be operated upon. The practice of operating to cure salpingitis in the acute stage is absolutely condemned. Nearly $\frac{1}{2}$ of such operations are unnecessary, if cases are first treated by palliative means. Furthermore, patients operated upon in the acute stage are subjected to unjustifiable morbidity and mortality, unnecessarily destructive surgery and to too high a percentage of unsatisfactory end results.

Heat Treatment. For many years the use of heat has been one of the most important palliative methods for the treatment of pelvic inflammations, but until comparatively recently it was used chiefly in the form of hot douches. With the advent of various types of electrical apparatus, as was to be expected, new methods of applying heat to the pelvic organs have been evolved. One of the most popular is the Elliott treatment, which supplies a hot water bag to the vagina under controlled conditions. Through the rubber bag, inserted into the vagina around the cervix, is circulated a current of hot water maintained at a constant temperature which is never allowed to go above 130° F. The average time for a treatment is 1 hour but this may be varied in accordance with the tolerance of the patient. This treatment causes a marked hyperemia in the pelvic tissues, an average increase of 17% in the leukocytes and an elevation in the temperature of the vagina, uterus, rectum, bladder and pelvic peritoneal cavity of from 5 to 7° and a profuse discharge from the cervix and vagina. Counseller,[6] trying this method at the Mayo Clinic, states that a high percentage of chronic infections of the pelvis can be clinically cured by it but that there is a fairly constant small percentage of cases in which operation will be required.

Randall[17] comments that there are cases of pelvic inflammation in which the vaginal bag does not radiate heat sufficiently to the affected viscera, either because of the inability of the patient to stand sufficient distention of the bag or by reason of the extent and situation of the infection. This is particularly true of parametritis with perirectal involvement and of high-lying tuboövarian infections. These pelvic conditions have recently been treated by means of a bag designed to apply heat through the rectum in addition to the usual vaginal application and from his experience this method of treatment seems to be of distinct advantage in hastening resolution. The applicator is constructed to permit sufficient distention to fill the lumen of the rectum,

so that heat can be applied to the structures lying anterior to the rectum. The bag is well lubricated and inserted into the rectum and pushed above the dentate margin before it is distended, otherwise the rectum will tend to expel the bag. The bag is distended with water at a pressure of between 2 and 3 pounds and the temperature is kept between 120 and 125° F. for 1 hour. It will cause some redness and edema of the rectal mucosa but no ulceration or necrosis. (All trauma should be avoided. Any form of bag which distends the vagina or rectum should be used with caution. Inflamed adnexa frequently become adherent posteriorly or in the cul-de-sac and forcible dilatation of either the vagina or rectum may result in liberation of pus and be followed by an exacerbation. C.C.N.)

The divergent opinions as to the therapeutic value of diathermy in the treatment of pelvic inflammatory disease may be due to variations in the technique of its application. Horowitz, Derow and Bierman[14] state that there is no method by means of which one may determine the degree of tissue heating which occurs during a diathermy treatment of the pelvis other than by direct thermal measurement. The reading of the milliameter is no direct guide, because the heat produced by the passage of the high-frequency current varies with the extent of the area of tissue in contact with the electrode, the shape of the electrode, the character of the tissues traversed by the current, the integrity of the local circulation, the effectiveness of the thermoregulatory mechanism of the patient as well as the duration of the current flow. The only way to know the temperatures obtained during a treatment is by actual measurement. These have been made by means of a vaginal electrode equipped with a thermometer. In 255 treatments, the average maximal temperature was 108.8° F. attained 19 minutes after the beginning of the treatment. At the end of treatment, usually after about 45 minutes, the vaginal temperature averaged 107.5° F., while the highest temperature recorded during any treatment was 112.5° F. By means of mercury thermometers in the cervix, bladder and rectum, the temperatures developed in these parts were found to follow closely the vaginal temperature, averaging but 1 or $1\frac{1}{2}$° lower. They believe, therefore, that the reading of the thermometer in the vaginal electrode is a true indication of the temperatures attained in adjacent tissues and also that "trans-pelvic diathermy" by external plate electrodes is effective as a method of pelvic heating.

In addition to the local application of heat by various means, there has been some work done of late in developing heat by means of fever therapy. In reporting their observations along this line, Desjardins, Stuhler and Popp[7] state that many observers have noted an inhibitory effect of high temperature on gonococcic infections. Experimental work of others which showed that a temperature of about 107° F. killed 99% of gonococci in 2 hours stimulated them to test the method in cases of gonorrhea, both acute and chronic, with or without complicating lesions. Of 29 patients treated, 25 were cured with complete cessation of urethral discharge, disappearance of symptoms and of gonococci in spite of repeated examinations. They are convinced that a large majority of female patients who have gonococcic infections can be cured by this method in much less time than by the methods previously used. Of course it should be remembered that a temperature of from

106 to 107° F. maintained for from 5 to 8 hours taxes the strength of the average individual to a considerable degree. If measures to prevent it were not taken, considerable loss of weight and strength would occur and would probably continue for several days. The loss of weight would result from the loss of fluids by perspiration, and the loss of strength would result chiefly from the loss of chlorides. This difficulty is obviated by causing the patients to drink, during each session of treatment, from 2 to 5 liters of a 0.6% solution of sodium chloride. As a result of this procedure, the weight of the average patient actually increases during a treatment session, and the incidental fatigue usually disappears within 24 hours. Their scheme of treatment is to raise the patient's rectal temperature to 106° F. and to maintain it between that and 107° F. for 6 hours at each of the two initial sessions of treatment, which are regarded as test sessions. If by this time the urethral discharge has ceased and gonococci have disappeared from smears, one or two additional sessions of fever are given in order to prevent any possibility of recurrence. If the discharge has not ceased after the second session, the subsequent sessions are extended to 7 or 8 hours, it seldom requiring more than four sessions to effect a cure. All of these treatments are carried out by means of the air-conditioned fever chamber known as the "Kettering hypertherm." Treatment of this kind requires the constant attention of nurse technicians, who must be carefully selected and specially trained. There must also be the constant supervision of a physician familiar with all the details of the method. The nurse must not leave the patient for an instant while the patient is in the chamber unless she is relieved by another nurse or physician.

A combination of systemic and local heating has been used with very satisfactory results by Bierman and Horowitz.[2] The technique they employ consists in the use of pelvic diathermy while the patient lies within a hood containing carbon filament lamps. By means of diathermy alone it is possible to maintain a temperature in the vagina of 108° F., which is 8° above the normal. The temperature of the cervix, as indicated by a thermocouple needle inserted into it, becomes elevated to within about 1.5° of the temperature registered by the vaginal electrode thermometer. The additional use of a cabinet surrounding the body, containing photothermal lamps, causes a rapid elevation of general body temperature, because of the prevention of heat loss from the body and the introduction of further heat energy into it. This combined use of heat by diathermy and photothermy is usually sufficient to cause an elevation of the mouth temperature to from 105 to 106° F., within 1½ hours. The vaginal temperature is then easily raised to 111 or 112° F., and these temperatures are maintained for from 3 to 4 hours. The sensations of the patient undergoing treatment are those usually experienced during hyperpyrexia induced by high-frequency currents. There is sometimes a sensation of pelvic warmth, but the patient is usually conscious only of a diffuse heating of the entire body. During the period of transition from normal temperature to 104° F. there is usually restlessness and general discomfort for which morphine or a barbiturate may be given but there is no pain at any time. They have wisely accepted for treatment only patients in good general condition, without cardiovascular or pulmonary disease or marked obesity. Treatments are not administered 4 days before the

expected menstruation, during the period, or for 3 days afterward. Pregnant patients have not been treated.

Other Non-operative Treatments. For several years certain investigators in Germany have been injecting living gonococci into patients suffering from gonorrhea. From a 4-year experience with this treatment, comprising over 300 injections, Schultz[19] states that there is no danger of a general septicemia from such a procedure, and he believes that while this form of treatment is not successful in every case it is a valuable addition to the therapy of gonorrhea. He warns that the treatment is contraindicated in the presence of a high temperature such as frequently accompanies acute pelvic inflammatory disease but the slight fever of subacute and chronic pelvic inflammatory disease may be disregarded. In his series 95% of the patients were in the chronic stage and of these 74% were discharged as cured after from 1 to 4 injections at 10-day intervals.

Believing that estrogenic substances stimulate the defensive mechanism of the pelvic organs, Fluhmann and Hoffmann[10] injected amniotin in a series of 29 adults with acute or chronic pelvic inflammatory disease. In 23 instances there were definite palpable adnexal masses at the time the treatment was begun. After the treatment, from 2 to 6 weeks later, complete healing with disappearance of the masses was noted in 7 cases while 9 others were improved but still had palpable masses. In 7 cases there was no improvement, of which 5 were subsequently operated upon. Of 6 patients who had no masses before treatment, only 3 showed any improvement from the treatment. While these results are interesting, the series is too small to be of much value, and besides many of these pelvic masses subside even if no treatment of any kind is given except rest.

The intramuscular injection of sterile milk is often of value as was stated in the beginning of this review. Greene[11] extols the value of this treatment and states that the injection of milk is followed by a leukocytosis, usually within 4 hours. He has found that the patients feel better, gain in weight and continue their routine work after the injections and major operations are sometimes avoided. Pre-operative injections of milk make operation somewhat less difficult and abbreviate the period of convalescence. In 18,270 injections given over a 5-year period there has been no evidence of untoward effect in any individual. In his work he used skimmed milk boiled for 20 minutes and allowed to cool. The first dose was 5 cc. injected intramuscularly and each subsequent dose is 10 cc. repeated at weekly intervals.

Since the most important principle in the non-operative treatment of pelvic inflammatory disease is the induction of pelvic hyperemia, Jacoby[15] proposes the use of one of the drugs recently made available which produce vasodilatation and thus induce hyperemia. He suggests the use of acetyl-beta-methylcholine-chloride which, when taken by mouth in doses of 100 to 200 mg., produces generalized flushing and sweating, increased salivation, a lowering of blood pressure, increase in pulse rate, intestinal peristalsis and metabolism, which last from ½ to 1 hour. Subcutaneously in doses of from 5 to 25 mg. the same effects are greatly increased except that the action on the gastrointestinal tract is less pronounced. When applied locally by iontophoresis, there is some general reaction but a much more pronounced

effect at the site of application. Of 10 patients treated in this manner, 7 were completely cured although they had extensive pelvic inflammation. He believes that this method is an effective agent in promoting the rapid absorption of inflammatory pelvic exudates with relief of symptoms and seems superior to other methods of exciting pelvic hyperemia because it has a much more sustained physiologic action. (Rest, preferably in the modified Fowler position, proper diet, avoidance of all trauma, and the non-traumatic application of heat are the sheet anchors of treatment of acute pelvic inflammatory disease and under this treatment the majority will subside. Too energetic treatment is unwise. C.C.N.)

Operative Treatment. It is often important, but at the same time sometimes difficult to differentiate between an acute salpingitis and an acute appendicitis. In a study of 19 cases of acute salpingitis and 38 of acute appendicitis, Smith, Harper and Watson[29] found that the sedimentation time of the blood may be of value in differentiating these two conditions, if the duration of symptoms when the test is made is taken into consideration. During the first 24 or even 48 hours after the onset of symptoms, the sedimentation time is apt to be shorter in acute salpingitis than in acute appendicitis; an occurrence that is not unfailing, but frequent enough to be given consideration, as it is more uniform than either the leukocyte count or the differential. They believe that this may be due to the difference in the two organs as regards their function and nerve supply. The appendix is supplied by both sympathetic and parasympathetic fibers. Gastro-intestinal symptoms occur for some time before there is any tenderness localized over the region of the appendix. Furthermore, the appendix is a vestigial organ capable of only slight distention before it causes symptoms. The Fallopian tube has only sympathetic nerve fibers and is a functioning organ which is capable of relatively great distensibility before causing symptoms. They show that with the duration of the infection the sedimentation time becomes shortened in the case of acute appendicitis and that is probably what happens also in acute salpingitis. But in the case of salpingitis the infection progresses further before giving symptoms. Therefore, the sedimentation time in acute salpingitis is shorter in the first 24 to 48 hours *after the onset of symptoms*, because the infection has been there many hours before it began to cause symptoms.

If acute appendicitis is present, of course immediate operation should be done, but if acute salpingitis is present, most gynecologists advise conservative non-operative treatment during the acute stage, as most of such cases subside. However, the occasion will arise when an abdomen is opened for acute appendicitis and acute salpingitis is found instead. What should be the proper procedure to follow under such circumstances? Conservatives advocate closure of the abdomen without disturbing the tubes; radicals advise extirpation of the tubes. The plan advocated by Elgart[8] is to ligate the abdominal ends of the tubes to prevent further contamination of the pelvic peritoneum. Following such operation the clinical signs rapidly improve; and, since the uterine ends of the tubes are open, there is good drainage at that point into the uterus and therefore no pyosalpinx will result. He has had occasion to see the results of such a procedure at secondary operations and found that the tubes remain slightly thickened. Of course such an operation

sterilizes the patient, but salpingitis frequently does also. If desired, a salpingostomy may be done at a later date to reëstablish the abdominal opening of the tube.

Halter[12] of Vienna states that the indications for operation in chronic pelvic inflammatory disease are: first that the patient shall have had at least 6 months conservative treatment without results, and second the expressed wish of the patient to be relieved by operation because of her painful symptoms. Operation is never performed until it is fairly certain that no latent infection exists, which means that the patient's temperature shall have been normal for at least 6 weeks and that the blood sedimentation test shows a rate over 1 hour. Of the patients admitted to this clinic only 9.2% were operated upon. Halter's study has shown that when operation is done better results will be obtained from the radical than from the conservative procedure. Thus the mortality of the radical operation was 1.7% as against 2.6% for the conservative procedure. With total removal of the pelvic organs 98.4% of the patients remain free from symptoms whereas only 42.1% of the patients who have had conservative operations are completely relieved. He believes that no patient should have a conservative operation who has cystic degeneration of both ovaries and he advises removal of a healthy tube if the opposite one is diseased, in order to forestall the later development of pain in the conserved organ, since the probability of pregnancy in these patients is slight, being only 10% in this series. In brief, his advice is "don't operate until you must and the patient is in good general condition, but when operation is done, make it radical." (There is no question as to the soundness of this advice as far as elderly women are concerned. In young women, bilateral salpingectomy and conservation of the ovaries and uterus, in properly selected cases, has given good results. Obviously cases should be carefully studied and individualized. No hard and fast rule will be suitable for all. C.C.N.)

Since tubal infections tend to sterilize themselves if reinfection can be prevented, Falk[9] proposes an operation which prevents reinfection and also conserves the tubes. The operation consists of resection of the cornual ends of both tubes thus interrupting the pathway of infection from the uterus to the tubes. In leaving the infected tube in the abdomen no fear is felt because since it cannot be reinfected it will undergo resolution. This operation has the advantage over salpingectomy in that there is less risk of interference with the ovarian circulation. In 75 cases in which the operation was performed, 67% were cured, 24% had slight residual symptoms and 7% had definite complaints after the operation.

Those familiar with pelvic inflammatory disease will recognize that a problem often arises in the management of those patients in whom subsidence of fever does not occur after proper treatment. In most cases sustained fever indicates active suppuration, and since laparotomy for the removal of affected structures carries an excessive mortality in cases of this type, it often becomes necessary to institute drainage. When drainage becomes necessary, Cooke[5] lists four possible means of approach, three of which are more or less orthodox. First may be mentioned the usual posterior colpotomy which has a very low mortality. Second, anterior colpotomy may be done in the occasional case in which the collection of pus lies anterior to the uterus or broad

ligament. Third, ordinary open laparotomy through uncontaminated peritoneal cavity may be done but this gives an almost prohibitive mortality. The last method which he mentions and has employed to advantage consists of approach by small incisions through the abdominal wall to areas of suppuration which are inaccessible by either of the vaginal routes. An effort is made to locate the incision over a point at which the parietal peritoneum is adherent to the underlying structures in order that the previously uncontaminated peritoneum may not be traversed. If the incision should enter the free peritoneal cavity, the site of adhesion of the inflammatory mass to the parietal peritoneum is located by digital exploration, the first incision is closed and a new incision is made over a safe point in the adherent area. If no point of adhesion is found, the parietal peritoneum is sutured to the diseased structures and the wound is packed with gauze; on the next day, the gauze is removed and the abscess is opened through the walled off sinus formed by this procedure. If desired, the diseased structures may be removed several weeks after drainage; but his experience has shown him that this secondary operation is often extremely difficult and that the patients who do not have the secondary operation often do better than those that are reoperated upon. Therefore he has practically abandoned secondary operation and advises against it.

Streptococcus Infection. It is now rather generally understood that while the gonococcus usually is the cause of salpingitis and tuboövarian abscesses, the streptococcus does not involve the lumen of the tubes but causes a pelvic lymphangitis or cellulitis and this is an extraperitoneal lesion. This disease process can terminate in one of three ways: if the virulence is very great the patient may soon die by the overwhelming toxemia; in many cases, the patient has sufficient resistance to overcome the infection and complete resolution occurs; in the third group, after a more or less stormy battle, the cellulitis undergoes abscess formation which requires surgical incision for its relief. Such an abscess may be opened by posterior colpotomy being careful not to invade the peritoneal cavity; but as Brady[3] points out in a lucid description of this subject, such an operation is beset with several dangers. If the forceps which is used to penetrate the broad ligament should perforate it there is immediately the danger of a streptococcic peritonitis. Moreover, in tunnelling the instrument laterally from the colpotomy incision toward the broad ligament there is danger of injury to the ureter or uterine artery. A second method of drainage is the inguinal route. This consists of making what amounts to a McBurney incision until the peritoneum is reached. The peritoneum is not opened but is pushed toward the median line and an extraperitoneal finger dissection is made until the diseased area in the broad ligament is reached. Brady prefers this matter method of drainage since these patients left the hospital on the average of 29 days after operation as against those drained by the vaginal route who remained in the hospital an average of 47 days after operation. Several of the patients in this series later became pregnant showing that this type of infection does not cause sterility but it is not safe for them to become pregnant too soon after such drainage because the streptococcus remains dormant in their tissues for quite some time and may cause a recurrence of the

cellulitis as a result of the congestion and stretching of the broad ligament which accompanies a pregnancy.

Other Types of Infection. Stein[21] calls attention to a safe and simple method of diagnosis and treatment of *tuberculous salpingitis*. Whenever this condition is suspected, he believes that it is advisable to use oxygen pneumoperitoneum for diagnostic roentgenography since oxygen will serve the additional purpose of being a valuable therapeutic agent. The patient usually shows prompt evidence of improvement, the temperature falls to normal within a few days, the pain is less, the patients feels stronger and begins to gain weight at once. In some instances a single insufflation suffices, in others repeated treatments are used in periods of from 4 days to 2 weeks. He recommends weekly insufflations of about 1 liter each, the number depending upon the results obtained. The patients are kept in bed from 18 to 24 hours after every injection for diagnostic purposes. In cases injected for therapeutic purposes they are usually bed patients in the beginning of treatment. When the temperature reaches normal they are kept in bed for 48 hours after each treatment. The rationale of this treatment is based upon the good results which have been obtained by exploratory laparotomy and exposure of the tissues to air. Pneumoperitoneum by the injection method spares the patient the danger and pain of a laparotomy. If no beneficial effects are noted after a fair trial, operation may still be done, the gas having done no harm. (The judicious use of the Roentgen-ray as recommended by the late Dr. J. O. Polak is worthy of a trial in cases of tuberculous salpingitis. C.C.N.)

Pneumococcus infection of the pelvic organs in women is discussed by Tompkins,[22] who reports 3 cases of this type. He states that the respiratory tract is the probable source of the pneumococci, but the route by which these organisms reach the peritoneal cavity is often a matter of conjecture. The two most likely possibilities are metastatic infection by either blood or lymph stream or ascending infection through the genital tract. The disease usually begins with a slight chill, sudden severe cramping lower abdominal pain, diarrhea and vomiting. High fever, high leukocytosis (30,000) with high neutrophil count (95%) and rapid pulse soon follow. Abdominal rigidity is often not marked. Abdominal distention and constipation often appear and are frequently accompanied by bulging in the cul-de-sac, because pneumococci rapidly produce large quantities of pus. Material for bacteriologic examination may be obtained by vaginal or abdominal puncture. The typical pus is profuse, thick and odorless and contains the organisms in pure culture. The prognosis of localized infections or abscesses that can be drained or removed *en masse* is good; but in other intraäbdominal pneumococcus infection the outlook is grave. The present trend of treatment of the generalized pneumococcus peritonitis is away from laparotomy in the hope that localization will occur. Specific remedies which have been suggested such as optochin, bile salts, autogenous vaccines and antipneumococcus serum have not been employed in a sufficient number of cases to permit evaluation.

King[16] reports that he has had 3 cases of this type and presents 11 additional ones which he has collected from the literature. There are two points which he emphasizes in the diagnosis. In many cases there

is often a previous indisposition usually associated with the symptoms of an upper respiratory infection and careful inquiry on this point should always be made. Another distinguishing point is the rapid formation of pus which takes place earlier and in far greater quantity than in peritonitis from other causes. Of course, pneumococcus peritonitis in children is by no means a rare condition but the condition which we are now considering in adult women has seldom been encountered.

A case of *blastomycosis* of the Fallopian tube and uterus has been reported by Hamblen, Baker and Martin[13] in a patient with arrested pulmonary blastomycosis. They were unable to find any similar case previously reported in the literature. The diagnosis was made from curettings and culture. The tissue reaction was much like that in tuberculosis except for the presence of the double-contoured blastomycetes. The treatment in this case consisted of radical removal of the diseased structures which was followed by an uncomplicated postoperative course.

Cancer of the Tubes. In reporting 2 cases of primary cancer of the tubes, Charache[4] reveals that he searched the literature and found that 323 such cases had been reported. It occurs in about 0.45% of all genital tumors and chronic inflammation is supposed to be a predisposing factor. Diagnosis is extremely difficult and is often missed even at operation unless the tumor is sectioned by the surgeon. As aids in diagnosis there are the presence of serosanguineous discharge with various menstrual disturbances, abdominal pain associated with a palpable adnexal tumor and a negative uterine curettage. The treatment of choice consists of radical surgery with removal of both tubes and ovaries and a complete hysterectomy with wide excision of the broad ligaments. This should be followed by Roentgen ray therapy. The prognosis is very poor, since only 7 cases in this collected series survived longer than 3 years.

Three cases of primary cancer of the Fallopian tubes are reported by Robinson[18] who states that this condition is frequently bilateral and therefore the apparently normal looking opposite tube should not deter us from removing the organs in a radical manner. The outer two-thirds of the tubes are the sites of greatest predilection. The fimbriated ends become closed late in the disease in contrast to what happens in salpingitis and then the tube may reach enormous proportions due to distention with secretions and necrotic tissue elements. The most common complaints are pain in the lower abdomen and yellow, watery or bloody vaginal discharges. The character of the pains is apt to be intermittent and they may disappear after a sudden gush of fluid from the vagina, in this respect resembling a hydrops tubæ profluens, which of course, is of inflammatory origin.

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PHYSIOLOGY

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Studies of Heart Muscle in Tissue Cultures. M. J. Hogue (Laboratory of Anatomy, University of Pennsylvania). Heart muscle from 8-day chick embryos was grown in tissue culture for 180 days. The medium was a combination of Locke and Tyrode solutions, chicken bouillon, and embryonic extract. In it 94.5% of the explants grew; 65.4% of these showed growth of muscle cells; 65% of the muscle-cell cultures contained cross striated myofibrillæ when fixed and stained. Myofibrillæ with striations were seen in living cultures and in the same preparations after they were fixed and stained. Most of the cardiac muscle cells were unicellular, a few were binuclear and a very few multinuclear.

The cardiac muscle cells showed great individual variations in their rate of contraction. The rate varied from 2 to 244 contractions per minute, depending largely on the temperature and the age of the culture, though other factors were involved. As the cultures cooled below 33° C. the beat became slower and finally stopped. The rate of contraction was most rapid in cultures from 15 to 60 days old. In older cultures the rate became slower. The oldest culture to beat was 158 days old.

Factors Concerned with the Toxic Action of Chloroform on the Liver. H. M. Vars, S. Goldschmidt, and I. S. Ravdin (Laboratory of Physiology and Harrison Department of Surgical Research, University of Pennsylvania). It has long been known that certain of the volatile anesthetics, notably chloroform, could produce damage of the liver following inhalation. Opie and Alford (1915) showed that a high-carbohydrate diet previous to the anesthesia afforded a degree of protection to the liver of rats which received chloroform. While a carbohydrate diet reduced the incidence of liver necrosis, a fat diet was found to increase the susceptibility of the liver to the damaging effects of this anesthetic. This observation was confirmed upon dogs by Davis and Whipple (1919). These findings have received further confirmation in our hands with both dogs and rats.

The protective action of a high-carbohydrate diet has generally been ascribed to the increase of liver glycogen which results from the diet. Our studies show that the principal cause of the protective action exerted by the increased liver glycogen is not the presence of the glycogen *per se*, but results from the reduction of liver lipid as a result of glycogen deposition on a high-carbohydrate diet. Within certain limits, the Rosenfeld hypothesis holds, namely an increase in liver glycogen is accompanied by a reduction in hepatic lipid. However, this rule is not invariable for we have been able by appropriate feeding to obtain animals in which the liver showed both a high-glycogen and a high-lipid content. As a result of these experiments we have concluded that, over a wide range, regardless of the liver glycogen content, if the fatty acids exceed a value in rats of between 15 and 20%, liver damage will usually result from the administration of chloroform.

The amount of liver lipid, therefore, conditions the amount of the fat-soluble chloroform which is taken up by the liver, and therefore determines the amount of the toxic agent present and the duration of the toxic action.

Identification of Blood by Hemolytic Methods. M. H. JACOBS, H. N. GLASSMAN, and A. K. PARPART (Laboratories of Physiology, University of Pennsylvania, and of Biology, Princeton University). Differences in the behavior of the erythrocytes of different species in solutions of certain penetrating substances are so great and so constant that frequently a given sample of blood may be identified by methods depending on osmotic hemolysis alone. The larger groups of vertebrates show characteristic differences in the relative rates of hemolysis in water and in appropriate solutions of ethylene glycol, glycerol and urea, respectively. Within a single class, such as the mammals, a further separation of species is possible by means of solutions of mannitol, erythritol, xylose, NH_4 tartrate, NH_4 borate and NH_4Cl, with and without NH_4 benzoate. By the use of these and certain additional characters such as the effects on permeability of $NaHCO_3$, CO_2, and traces of Cu, the direct hemolytic effects of bicarbonates, and differences in osmotic resistance in solutions of NaCl and KCl, it has been found possible to construct an analytical key which permits the identification of all of the 20 species of mammals that have so far been carefully studied. The fact that species are so readily distinguishable by characters of this sort indicates a high degree of specificity in the constitution of the cell surface which has important consequences for theories of cell permeability.

The Effects of 10 Commonly Used Drugs on Basal Cardiac Output, Metabolism, Blood Pressure, Heart Size, Respiration, and the Electrocardiogram in Over 100 Patients. C. J. GAMBLE, I. STARR, A. MARGOLIES, J. S., DONAL, JR., N. JOSEPH, and E. EAGLE (Departments of Research Therapeutics, Pharmacology, Robinette Foundation, and Medical Division of the Hospital, University of Pennsylvania). The action of commonly used drugs on the cardiac output, size, and rate, on the blood pressure, on the metabolic rate, on the respiration, and on the electrocardiogram has been ascertained and described.

The subjects consisted of over 100 patients suffering chiefly from cardiac or circulatory disease but not from congestive heart failure. Estimations were made under conditions of basal metabolism. The results have been subjected to statistical analysis.

The drugs studied included digitalis, epinephrine, ephedrine, caffeine, theophylline, carbaminoylcholine, sodium nitrite, nitroglycerine, pitressin, quinidine, morphine and strychnine.

The action of these drugs is almost altogether similar to expectations based on animal experiments.

Pancreatectomy in the Pig. F. D. W. Lukens (Cox Institute for Metabolic Research, University of Pennsylvania). Nine young pigs, weighing 5 to 15 kg., were depancreatized. The average survival was 9 days. When fasted, glycosuria was slight or absent, and the nitrogen excretion, although double that of fasted controls, was low. Ingested carbohydrate was quantitatively excreted. Ketonuria was marked but was not associated with acidosis. The injection of crude alkaline pituitary extracts caused death in acidosis and coma with greatly increased serum lipoids.

The results have been compared with pancreatic diabetes in other species and with the findings in Houssay animals. Pancreatic diabetes may differ from the picture seen in the dog (*a*) by the selection of species or (*b*) by the simultaneous removal of other endocrine glands in a single species. The suggestion is offered that the apparently mild diabetes of the pig is due to the nature of its pituitary (or other endocrine) function rather than to the utilization of carbohydrate in the absence of insulin.

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